PB92-205665

Dermal Exposure Assessment: Principles and Applications

Versar, Inc., Springfield, VA

Prepared for:

Environmental Protection Agency, Washington, DC

Jan 92

U.S. Department of Commerce
National Technical Information Service
NTIS

TECHNICAL REPORT DATA

(Please read Instructions on the reverse before completing)

1. REPORT NO. EPA/600/8-91/011B	2.	3. REC PB92-205665
4. TITLE AND SUBTITLE Dermal Exposure Assessment: Principles and Applications		5. REPORT DATE September 1991
		6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S) See Authors Page		8. PERFORMING ORGANIZATION REPORT NO. OHEA-E-367
9. PERFORMING ORGANIZATION NAME AND ADDRESS Versar Inc.		10. PROGRAM ELEMENT NO. Y105/H/01/02
		11. CONTRACT/GRANT NO. 68-D00101
12. SPONSORING AGENCY NAME AND ADDRESS Office of Health & Environmental Assessment Exposure Assessment Group (RD-689) U.S. Environmental Protection Agency Washington, DC 20460		13. TYPE OF REPORT AND PERIOD COVERED Report
		14. SPONSORING AGENCY CODE EPA/600/021
15. SUPPLEMENTARY NOTES		

16. ABSTRACT

The purpose of this document is to describe the principles of dermal absorption and show how to apply these principles in actual human exposure scenarios. The primary focus of the document is on dermal contact with water, soils and vapors. For each of these media, the experimental data on the dermal properties of specific compounds are summarized and methods are provided for predicting these properties when data is lacking. Additionally, scenario factors describing the frequency, duration and intensity of contact are presented for the soil and water media.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT Release to the Public	19. SECURITY CLASS *(This Report)* Unclassified	21. NO. OF PAGES 355
	20. SECURITY CLASS *(This page)* Unclassified	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

United States
Environmental Protection
Agency

Office of Research and
Development
Washington, DC 20460

EPA/600/8-91/011B
January 1992

EPA

Dermal Exposure Assessment: Principles and Applications

Interim Report

PB92-205665

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL INFORMATION SERVICE
SPRINGFIELD, VA 22161

EPA/600/8-91/011B
January 1992
Interim Report

DERMAL EXPOSURE ASSESSMENT: PRINCIPLES AND APPLICATIONS

Exposure Assessment Group
Office of Health and Environmental Assessment
U.S. Environmental Protection Agency
Washington, D.C. 20460

Printed on Recycled Paper

DISCLAIMER

This document is an interim report subject to review by the Science Advisory Board. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

CONTENTS

Tables viii

Figures xii

Foreword xiii

Preface xiv

Authors and Reviewers xv

Acknowledgements xviii

Symbols xvix

1. INTRODUCTION 1-1

PART 1. PRINCIPLES OF DERMAL EXPOSURE ASSESSMENT 2-1

2. MECHANISMS OF DERMAL ABSORPTION 2-1
  2.1. STRUCTURE AND FUNCTION OF THE SKIN 2-1
  2.2. FATE OF COMPOUNDS APPLIED TO THE SKIN 2-5
    2.2.1. Transport Processes Occurring in the Skin 2-5
    2.2.2. Loss Processes Occurring in the Skin 2-8
      2.2.2.1. *Evaporation from the Surface of the Skin* 2-8
      2.2.2.2. *Binding of Compounds in the Skin* 2-9
      2.2.2.3. *Metabolism* 2-10
  2.3. FACTORS THAT INFLUENCE PERCUTANEOUS ABSORPTION 2-13
    2.3.1. Skin-Specific Factors 2-13
      2.3.1.1. *Site of Application or Exposure* 2-13
      2.3.1.2. *Age of the Skin* 2-19
      2.3.1.3. *Skin Condition* 2-21
      2.3.1.4. *Hydration* 2-23
      2.3.1.5. *Circulation to the Skin* 2-23
      2.3.1.6. *Skin Temperature* 2-24
      2.3.1.7. *Miscellaneous Factors* 2-26
    2.3.2. Compound-Specific Factors 2-26
      2.3.2.1. *Partition Coefficients* 2-26
      2.3.2.2. *Polarity* 2-28
      2.3.2.3. *Chemical Structure* 2-30
      2.3.2.4. *Volatility* 2-31
      2.3.2.5. *Compound Concentration* 2-32
  2.4. SUMMARY AND CONCLUSIONS 2-33
    2.4.1. Structure 2-34

CONTENTS (continued)

Page

2.4.2. Fate 2-34
2.4.3. Factors 2-35

3. TECHNIQUES FOR MEASURING DERMAL ABSORPTION 3-1
3.1. IN VIVO STUDIES 3-3
3.1.1. Quantification of Radioactivity, Parent Compound, or Metabolite Levels in Excreta (Indirect Method) 3-4
3.1.2. Quantitation of Radioactivity, Parent Compound, or Metabolite Levels in Excreta, Air, and Tissues (Direct Method) 3-5
3.1.3. Quantification of Parent Compound or Metabolite in Blood, Plasma, or Tissues 3-5
3.1.4. Quantification of the Disappearance of the Compound from the Surface of the Skin or from the Donor Solution 3-6
3.1.5. Measurement of a Biological Response 3-7
3.1.6. Stripping Method 3-8
3.2. IN VITRO TECHNIQUES 3-9
3.2.1. Diffusion Cells 3-10
3.2.2. Isolated Perfused Tubed-Skin Preparation 3-17
3.2.3. Stratum Corneum Binding Technique 3-18
3.3. COMPARISON OF IN VITRO AND IN VIVO PERCUTANEOUS ABSORPTION VALUES 3-19
3.4. INTERSPECIES COMPARISON OF PERCUTANEOUS ABSORPTION VALUES 3-21
3.5. SUMMARY, CONCLUSIONS, AND RESEARCH RECOMMENDATIONS 3-26

4. MATHEMATICAL DESCRIPTION OF DERMAL ABSORPTION 4-1
4.1. THEORETICAL BASIS OF K_P AND J_{SS} VALUES 4-3
4.2. DERMAL (PERCUTANEOUS) ABSORPTION RATE EQUATION PARAMETERS 4-5
4.2.1. Partition Coefficient 4-5
4.2.2. Pathlength of Chemical Diffusion 4-9
4.2.3. Diffusion Coefficient 4-10
4.2.4. Concentration Gradient 4-11
4.3. EVALUATION OF PERMEABILITY COEFFICIENTS $K_{P,S}$ FROM EXPERIMENTAL STUDIES 4-12
4.3.1. In Vitro Approaches 4-12
4.3.2. In Vivo Approaches 4-15
4.4. DEFINITIONS OF PERMEABILITY COEFFICIENTS WHEN THE MEDIUM IS NOT WATER 4-17
4.4.1. Nonaqueous Solvent 4-18
4.4.2. Pure Liquid 4-19
4.4.3. Vapor Phase 4-19
4.4.4. Soil 4-20

CONTENTS (continued)

Page

2.4.2. Fate 2-34
2.4.3. Factors 2-35

3. TECHNIQUES FOR MEASURING DERMAL ABSORPTION 3-1
3.1. IN VIVO STUDIES 3-3
3.1.1. Quantification of Radioactivity, Parent Compound, or Metabolite Levels in Excreta (Indirect Method) 3-4
3.1.2. Quantitation of Radioactivity, Parent Compound, or Metabolite Levels in Excreta, Air, and Tissues (Direct Method) 3-5
3.1.3. Quantification of Parent Compound or Metabolite in Blood, Plasma, or Tissues 3-5
3.1.4. Quantification of the Disappearance of the Compound from the Surface of the Skin or from the Donor Solution 3-6
3.1.5. Measurement of a Biological Response 3-7
3.1.6. Stripping Method 3-8
3.2. IN VITRO TECHNIQUES 3-9
3.2.1. Diffusion Cells 3-10
3.2.2. Isolated Perfused Tubed-Skin Preparation 3-17
3.2.3. Stratum Corneum Binding Technique 3-18
3.3. COMPARISON OF IN VITRO AND IN VIVO PERCUTANEOUS ABSORPTION VALUES 3-19
3.4. INTERSPECIES COMPARISON OF PERCUTANEOUS ABSORPTION VALUES 3-21
3.5. SUMMARY, CONCLUSIONS, AND RESEARCH RECOMMENDATIONS 3-26

4. MATHEMATICAL DESCRIPTION OF DERMAL ABSORPTION 4-1
4.1. THEORETICAL BASIS OF K_P AND J_{SS} VALUES 4-3
4.2. DERMAL (PERCUTANEOUS) ABSORPTION RATE EQUATION PARAMETERS 4-5
4.2.1. Partition Coefficient 4-5
4.2.2. Pathlength of Chemical Diffusion 4-9
4.2.3. Diffusion Coefficient 4-10
4.2.4. Concentration Gradient 4-11
4.3. EVALUATION OF PERMEABILITY COEFFICIENTS $K_{P,S}$ FROM EXPERIMENTAL STUDIES 4-12
4.3.1. In Vitro Approaches 4-12
4.3.2. In Vivo Approaches 4-15
4.4. DEFINITIONS OF PERMEABILITY COEFFICIENTS WHEN THE MEDIUM IS NOT WATER 4-17
4.4.1. Nonaqueous Solvent 4-18
4.4.2. Pure Liquid 4-19
4.4.3. Vapor Phase 4-19
4.4.4. Soil 4-20

CONTENTS (continued)

Page

4.5. THE VALUE OF THE LIMITING $K_{P,S}$ FOR CHEMICALS OF HIGH LIPOPHILICITY 4-20
4.6. ESTIMATION OF ABSORBED DOSE 4-22

5. DERMAL ABSORPTION OF COMPOUNDS FROM WATER 5-1
  5.1. EXPERIMENTALLY DERIVED K_p VALUES 5-1
    5.1.1. Strategy for Reviewing Experimental Data 5-1
    5.1.2. Recommended K_p Values 5-8
  5.2. METHODS FOR PREDICTING PERMEABILITY COEFFICIENT OF AQUEOUS CONTAMINANTS 5-11
    5.2.1. Empirical Correlations 5-11
    5.2.2. Theoretical Skin Permeation Models 5-21
      5.2.2.1. Scheuplein Laminate Model with Parallel Follicular Pathway 5-33
      5.2.2.2. Michaels' Two-Phase Model for Stratum Corneum 5-33
      5.2.2.3. Two Parallel Pathway Model 5-34
      5.2.2.4. Albery and Hadgraft Model 5-34
      5.2.2.5. Kasting, Smith, and Cooper Model 5-35
    5.2.3. Statistical Algorithms for K_p Based on Literature Data 5-38
    5.2.4. Conclusions for How to Predict K_p Values 5-37
  5.3. ESTIMATING THE DERMALLY ABSORBED DOSE PER EVENT 5-47
    5.3.1. Estimating DA_{event} for Inorganics 5-48
    5.3.2 Estimating DA_{event} for Organics 5-49

APPENDIX: SUMMARY OF COMPOUND-SPECIFIC K_p DATA 5-65

6. DERMAL ABSORPTION OF COMPOUNDS FROM SOIL 6-1
  6.1. FACTORS AFFECTING THE DERMAL (PERCUTANEOUS) ABSORPTION OF COMPOUNDS FROM SOIL 6-2
  6.2. USING EXPERIMENTALLY DERIVED VALUES 6-9
    6.2.1. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) 6-11
      6.2.1.1. *Experimental Results* 6-11
      6.2.1.2. *Analysis of Data* 6-18
    6.2.2. 3,3′,4,4′-Tetrachlorobiphenyl (TCB) 6-19
      6.2.2.1. *Experimental Results* 6-20
      6.2.2.2. *Analysis of Data* 6-21
    6.2.3. Benzo[a]Pyrene (BaP) 6-22
      6.2.3.1. *Experimental Results* 6-23
      6.2.3.2. *Analysis of Data* 6-24
    6.2.4. DDT 6-25
      6.2.4.1. *Experimental Results* 6-26
      6.2.4.2. *Analysis of Data* 6-26
    6.2.5. Cadmium 6-27
      6.2.5.1. *Experimental Results* 6-27

CONTENTS (continued)

Page

6.2.5.2. *Analysis of Data* 6-28
6.2.6. Benzene, Toluene, and Xylene 6-28
6.2.7. Hexadecane 6-28

6.3. PREDICTIVE APPROACHES TO ESTIMATING DERMAL UPTAKE 6-29
6.3.1. Use of Structural Analogues 6-30
6.3.2. Upper Bounding Estimates of Dermal Bioavailability and Percutaneous Absorption 6-32
6.3.2.1. *Data on Absorption from Other Vehicles* 6-33
6.3.2.2. *Soil Extraction Data* 6-34
6.3.2.3. *Combined Upper Bounding Estimate* 6-35
6.3.2.4. *Data on Oral Bioavailability* 6-35
6.3.3. Theoretical Modeling of Percutaneous Absorption from Soil 6-36
6.4. ESTIMATION OF DERMALLY ABSORBED DOSE 6-43

7. DERMAL ABSORPTION OF CHEMICAL VAPORS 7-1
7.1. FACTORS AFFECTING THE DERMAL ABSORPTION OF VAPORS 7-2
7.1.1. Chemical Characteristics 7-3
7.1.2. Chemical-Biological Parameters 7-4
7.1.3. Biological Parameters 7-5
7.1.4. Exposure Parameters 7-5
7.2. EXPERIMENTALLY DERIVED VALUES 7-7
7.2.1. Human In Vivo 7-7
7.2.2. Human In Vitro 7-10
7.2.3. Primates In Vivo 7-13
7.2.4. Rodents In Vivo 7-13
7.3. EQUATIONS FOR ESTIMATING THE DERMAL ABSORPTION OF CHEMICAL VAPORS 7-16
7.3.1. When Permeability Constant Is Available 7-16
7.3.2. When Permeability Constant Is Not Available but Flux or Total Absorbed Is Available 7-21
7.3.3. When No Permeability Data Are Available 7-21
7.4. DECISION TREE FOR RISK CHARACTERIZATION OF TOXICITY DUE TO DERMAL ABSORPTION OF CHEMICAL VAPORS 7-22
7.4.1. Determination of Maximum Achievable Concentration 7-22
7.4.2. Determination of Permeability Constant 7-24
7.4.3. Potential for Contact Site Toxicity 7-25
7.4.4. Choice of Health Risk Estimates 7-26
7.4.5. Risk Characterization 7-27
7.5. RISK CHARACTERIZATION CASE STUDY OF N-HEXANE 7-27
7.5.1. Determination of Maximum Achievable Concentration 7-27
7.5.2. Determination of Permeability Constant 7-29
7.5.3. Dose Estimation 7-29

CONTENTS (continued)

Page

7.5.4. Choice of Health Risk Estimate 7-30
7.5.5. Risk Characterization 7-31

CHAPTER 7 APPENDIX: CALCULATION OF VAPOR PRESSURE 7-32

PART 2. APPLICATIONS OF DERMAL EXPOSURE ASSESSMENT 8-1

8. CHARACTERIZING DERMAL EXPOSURE SCENARIOS 8-1
8.1. EXPOSED POPULATIONS 8-3
8.2. CONTAMINATION OF ENVIRONMENTAL MEDIA 8-3
8.3. EXPOSURE TIME, FREQUENCY, AND DURATION 8-4
8.3.1. Soil Contact Time, Frequency, and Duration 8-4
8.3.2. Water Contact Time, Frequency, and Duration 8-7
8.4. SKIN SURFACE AREA 8-8
8.5. DERMAL ADHERENCE OF SOIL 8-13
8.5.1. Review of Experimental Data 8-13
8.5.2. The Soil "Monolayer" Concept 8-17
8.6. METHODS FOR MEASURING DERMAL EXPOSURE 8-18
8.7. SUMMARY AND CONCLUSIONS 8-19

9. RELATIVE CONTRIBUTION OF DERMAL EXPOSURE TO TOTAL ABSORBED DOSE 9-1
9.1. GENERAL CONSIDERATIONS FOR DETERMINING IMPORTANCE OF DERMAL ROUTE 9-1
9.2. CONTRIBUTION OF DERMAL EXPOSURE TO THE TOTAL ABSORBED DOSE OF NEAT COMPOUNDS 9-5
9.3. CONTRIBUTION OF DERMAL EXPOSURE TO THE TOTAL ABSORBED DOSE OF COMPOUNDS IN AQUEOUS MEDIA 9-6
9.4. CONTRIBUTION OF DERMAL EXPOSURE TO THE TOTAL ABSORBED DOSE OF CHEMICAL VAPORS 9-20
9.5. CONTRIBUTION OF DERMAL EXPOSURE TO THE TOTAL ABSORBED DOSE OF COMPOUNDS IN THE SOIL 9-23
9.6. SUMMARY OF CONDITIONS THAT ENABLE DERMAL UPTAKE TO BECOME A SIGNIFICANT ROUTE OF EXPOSURE 9-26

10. STEPWISE DERMAL EXPOSURE ASSESSMENT PROCESS 10-1
10.1. CONTACT WITH COMPOUNDS IN AQUEOUS MEDIA 10-2
10.2. CONTACT WITH COMPOUNDS IN SOIL 10-6
10.3. USE OF DERMAL ABSORPTION DATA IN RISK ASSESSMENT 10-9

GLOSSARY G-1

REFERENCES R-1

TABLES

Page

Table 2-1 Evidence for the Two-Phase Model of the Stratum Corneum 2-4

Table 2-2 Comparison of Vapor Pressure and Disposition of Radioactivity After Topical Application of Radiolabeled Control Compounds to Pig Skin Under Standardized Conditions 2-9

Table 2-3 Effect of Anatomical Region on In Vivo Percutaneous Absorption of Pesticides in Humans 2-15

Table 2-4 Percutaneous Absorption in Monkeys as Related to Site of Application and Test Compound 2-16

Table 2-5 Effect of Gender and Body Site on the Permeability of Rat Skin 2-17

Table 2-6 Rat Skin Thickness Measurement from Frozen Sections 2-18

Table 2-7 Regional Variation in Stratum Corneum Thickness in Humans 2-19

Table 2-8 In Vitro Percutaneous Absorption of Triclocarban in Human Adult and Newborn Abdominal and Foreskin Epidermis 2-20

Table 2-9 Effect of Temperature on Permeability Coefficients for Model Compounds Permeating Hairless Mouse Skin In Vitro 2-25

Table 2-10 In Vitro Permeability Coefficients and Partition Data for Various Phenol Compounds 2-27

Table 2-11 Permeability of Hairless Mouse Skin to Selected Phenols as a Function of pH 2-30

Table 2-12 Permeability of Human Skin (In Vitro) to Alcohols 2-31

Table 2-13 Percutaneous Absorption of Topical Doses of Several Compounds in the Rhesus Monkey 2-33

Table 3-1 Experimental Techniques Used to Obtain K_p or Percent Absorbed Values 3-2

Table 3-2 Comparison of In Vivo Methods for Determining Mean Bioavailability 3-6

Table 3-3 In Vitro Percutaneous Absorption of Triclocarban in Human Adult Abdominal Epidermis 3-12

TABLES (continued)

Page

Table 3-4 Effect of Receptor Fluid Composition on the Relative Absorption of Hydrophobic Compounds 3-13

Table 3-5 Percutaneous Absorption of Radiolabeled Compounds on Pig Skin In Vitro and In Vivo 3-15

Table 3-6 Influence of the Epidermis on Percutaneous Absorption of Compounds Through Pig Skin 3-16

Table 3-7 Total Absorption of Various Compounds by Skin In Vivo and In Vitro (Modified Tests) 3-19

Table 3-8 Ranking of the Relative In Vitro Percutaneous Absorption of Different Species 3-22

Table 3-9 Permeability of Animal Skin Relative to Human Skin 3-23

Table 3-10 Percutaneous Absorption of Nitroaromatic Compounds in Human and Monkey Skin 3-24

Table 3-11 Relative In Vitro Percutaneous Absorption of Water and Paraquat Through Human and Animal Skin 3-25

Table 3-12 Summary of Factors That May Affect the Use of K_p Data in Cutaneous Exposure Assessment 3-27

Table 5-1 Weight of Evidence Scoring System 5-5

Table 5-2 Second Order and Statistical Criteria for Reviewing K_p Data 5-8

Table 5-3 Permeability Coefficient Values for Compounds in Aqueous Media 5-9

Table 5-4 Permeability Coefficients for Human Skin (Aqueous Solutions) and Octanol/Water Partition Coefficients (Neat) of Organic Compounds 5-15

Table 5-5 Algorithms for Calculating Permeability Coefficients from Octanol/Water Coefficients 5-20

Table 5-6 Regression Equations Developed by Various Authors 5-22

Table 5-7 Predicted K_p Estimates for Common Pollutants 5-39

Table 5-8 K_p, τ and t^* Estimates for Common Pollutants 5-53

TABLES (continued)

Page

Table 6-1 Properties of Soil Used in Studies of Dermal Absorption of TCDD From Two Types of Soil 6-8

Table 6-2 Dermal Absorption of Soil-Adhered Organic Compounds 6-12

Table 6-3 Recommended Percentages of Applied Dose Absorbed for Soil Applications of 0.2 mg/cm^2 - 1.0 mg/cm^2 and Exposure Less than or Equal to 24 Hours 6-14

Table 6-4 Absorption of TCDD Over Time 6-17

Table 6-5 Absorption of TCB Over Time 6-21

Table 7-1 Estimated Human Permeability Constants for Vapor Phase Organic Chemicals 7-8

Table 7-2 Estimated Permeability Coefficient Values (cm/hour) for Alcohol and Alkane. Saturated Vapors 7-11

Table 7-3 Flux and Permeability Coefficient Values for Permeant Gases in Humans 7-11

Table 7-4 Flux Values for Organic Compounds Permeating Human Skin In Vitro as a Saturated Vapor and as a Liquid 7-12

Table 7-5 Dermal Vapor Absorption in Rats In Vivo 7-14

Table 7-6 Vapor Permeability Constants in Rodents 7-15

Table 7-7 Estimated K_p^{air} Values Calculated From Fat/Air Partition Coefficient Data 7-17

Table 8-1 Assumptions of Outdoor Soil Exposure Time 8-5

Table 8-2 Assumptions of Frequency of Exposure to Soil 8-6

Table 8-3 Surface Area by Body Part for Adults (m^2) 8-11

Table 8-4 Total Body Surface Area of Male Children in Square Meters 8-12

Table 8-5 Soil Adherence Values 8-16

Table 8-6 Range of Recommended Defaults for Dermal Exposure Factors 8-20

Table 9-1 Estimation of PEA and EEA Uptake in Man 9-6

Table 9-2 Relative Contribution (%) of Dermal and Oral Exposure to Dose 9-9

TABLES (continued)

Page

Table 9-3 Absorption Constants (Fraction Absorbed) for Various Routes of Exposure 9-10

Table 9-4 Effect of Drinking Water Concentration on Relative Exposure Via All Routes to a Child's Total Body Burdens in Summer (Rural)[a] 9-11

Table 9-5 Lifetime Equivalent Exposure Factors (Expressed as Percent of Total Exposure) for Trans-1,2-Dichloroethylene in Tap Water 9-12

Table 9-6 Relative Contribution of Different Routes of Exposure to the Absorbed Dose of VOCs in Drinking Water 9-15

Table 9-7 Assumed Minimum and Maximum Conditions for Dermal Absorption as Defined by Brown and Hattis (1989) 9-16

Table 9-8 Contribution of Skin Uptake to the Total Absorbed Dose of Chemical Vapors in the Rat 9-22

Table 10-1 Default Values for Water-Contact Exposure Parameters 10-3

Table 10-2 Default Values for Soil 10-6

FIGURES

Page

Figure 1-1 Dermal Risk Assessment Process 1-3

Figure 2-1 Structure of the Skin 2-3

Figure 2-2 Two-Phase Model of the Stratum Corneum 2-3

Figure 2-3 Transport/Loss Processes Occurring in the Skin 2-6

Figure 2-4 Major Routes of Diffusion Through the Skin 2-7

Figure 2-5 Regional Variation in the Percutaneous Absorption of Hydrocortisone in Humans . 2-14

Figure 3-1 IPPSF Preparation and Perfusion System 3-18

Figure 4-1 An Example of a Physiologically-based Pharmacokinetic Model 4-16

Figure 4-2 Cumulative Amount of Chemical Fluxing Out of the Stratum Corneum as a Function of Time 4-23

Figure 4-3 Cumulative Amount of Chemical Fluxing Into and Out of the Stratum Corneum as a Function of Time 4-23

Figure 4-4 Cumulative Mass of Chemical Entering the Stratum Corneum Including the Viable Epidermis 4-26

Figure 7-1 Decision Tree for Risk Characterization of Toxicity Due to Dermal Absorption . . 7-23

Figure 7-2 Empirical Basis for Trouton's Rule 7-33

Figure 7-3 Variation of Vapor Pressure with Temperature 7-34

Figure 9-1 Decision Matrix to Evaluate Importance of Dermal Exposure 9-2

Figure 9-2 Ratio of Dermal to Ingested Dose as a Function of K_p 9-19

FOREWORD

The Exposure Assessment Group (EAG) within the Office of Health and Environmental Assessment of EPA's Office of Research and Development has three main functions: (1) to conduct exposure assessments; (2) to review assessments and related documents; and (3) to develop guidelines for exposure assessments. The activities under each of these functions are supported by and respond to the needs of the various program offices. In relation to the third function, EAG sponsors projects aimed at developing or refining techniques used in exposure assessments.

The purpose of this document is to describe the principles of dermal absorption and show how to apply these principles in actual human exposure scenarios. These procedures are not official Agency guidance, rather they represent the judgements of the authors and are offered as a starting point for Agency programs to adopt/modify in light of programmatic considerations.

Historically, EPA has given highest priority to addressing human exposures associated with ingestion and inhalation. This reflected the belief that dermal exposures are less important and that much less is known about dermal exposure to environmental pollutants. However, the importance of dermal toxicity has long been recognized in other fields such as cosmetics and drugs. As a result of research in these fields, the state of the science has progressed steadily and a considerable knowledge base has developed. This document represents one of the first to comprehensively describe the state-of-the-science and how it can be applied to human exposure scenarios involving environmental pollutants. Much uncertainty remains regarding the importance of dermal exposure and how to best evaluate it. However, we believe that this document will help develop a better understanding of these challenging issues.

Michael A. Callahan
Director
Exposure Assessment Group

PREFACE

The Exposure Assessment Group of the Office of Health and Environmental Assessment has prepared this guidance document at the request of the Office of Emergency and Remedial Response (Superfund) of the Office of Solid Waste and Emergency Response.

The purpose of this document is to describe the principles of dermal absorption and show how to apply these principles in actual human exposure scenarios. The literature search supporting this document is current to 1992.

NOTE TO READER: The earlier drafts of this document were titled "Interim Guidance for Dermal Exposure Assessment." The title was changed in response to comments received at the April 1991 Peer Review Workshop.

AUTHORS AND REVIEWERS

The Exposure Assessment Group (EAG) within EPA's Office of Health and Environmental Assessment was responsible for the preparation of this document. The first draft was prepared by Technical Resources, Inc. under EPA contract number 68-W8-0082. Revisions and additional preparation were provided by an expert workgroup with the support of ILSI Risk Science Institute under EPA Cooperative Agreement Number CR-817457-01-0 and VERSAR Inc. under EPA contract number 68-D0 0101. Kim Hoang of EAG served as EPA task manager (as well as contributing author) providing overall direction and coordination of the production effort as well as technical assistance and guidance.

TASK MANAGER

Kim-Chi T. Hoang	EPA, Office of Health and Environmental Assessment

AUTHORS

Robert Bronaugh	FDA, Center for Food Safety and Applied Nutrition
Ronald Brown	Technical Resources, Inc.
Annette Bunge	Colorado School of Mines
Jeffrey Driver	Versar Inc.
Gordon Flynn	University of Michigan
Bentley Gregg	Versar Inc.
Richard Guy	University of California, San Francisco
Karen Hammerstrom	EPA, Office of Health and Environmental Assessment
Kim-Chi T. Hoang	EPA, Office of Health and Environmental Assessment
Annie Jarabek	EPA, Office of Health and Environmental Assessment
Russell Kinerson	EPA, Office of Health and Environmental Assessment
Frank Marzulli	Consultant in Toxicology
Major James McDougal	Wright Patterson Air Force Base
Nica Mostaghim	Versar Inc.
John Schaum	EPA, Office of Health and Environmental Assessment

REVIEWERS

Preliminary drafts of this document have received extensive internal and external review. In addition, a peer-review workshop was held on April 2 and 3, 1991. Participants at this workshop were:

Environmental Protection Agency Reviewers:

Linda Birnbaum	Office of Health Research
Jerry Blancato	Office of Modeling, Monitoring Systems, and Quality Assurance
Timothy Buckley	Atmospheric Research and Exposure Laboratory
Nancy Chiu	Office of Drinking Water
Christina Cinalli	Office of Toxic Substances
Ernest Falke	Office of Toxic Substances
Larry Hall	Office of Health Research
Karen Hammerstrom	Office of Health and Environmental Assessment
Kim Hoang	Office of Health and Environmental Assessment
Annie Jarabek	Office of Health and Environmental Assessment
Leonard Keifer	Office of Toxic Substances
Carole Kimmel	Office of Health and Environmental Assessment
Russell Kinerson	Office of Health and Environmental Assessment
Steven Knott	Office of Pesticide Programs
Jim Konz	Office of Emergency and Remedial Response
Terry O'Bryan	Office of Emergency and Remedial Response
Bruce Peirano	Office of Health and Environmental Assessment
John Schaum	Office of Health and Environmental Assessment
Dharm Singh	Office of Health and Environmental Assessment
Babasaheb Sonawane	Office of Health and Environmental Assessment
Robert Zendzian	Office of Pesticide Programs

Other Government Agency Reviewers:

Robert Bronaugh	FDA, Center for Food Safety and Applied Nutrition
Claire Franklin	Health & Welfare Canada
Major James McDougal	Wright Patterson Air Force Base
Thomas McKone	Lawrence Livermore National Laboratory
William Reifenrath	Letterman Army Institute of Research
Janet Springer	FDA, Center for Food Safety and Applied Nutrition
Curtis Travis	Oak Ridge National Laboratory

EPA Contractor Reviewers:

Ron Brown	Technical Resources, Inc.
Jeffrey Driver	Versar, Inc.
Larry Fishbein	ILSI Risk Science Institute
Carol Henry	ILSI Risk Science Institute
Frank Marzulli	Consultant in Toxicology
Abe Mittelman	Technical Resources, Inc.
Gary Whitmyre	Versar, Inc.

Academic Reviewers:

Kenneth B. Bischoff	University of Delaware
Annette Bunge	Colorado School of Mines
Halina Brown	Clark University
Yie Chen	Rutgers University
Gordon Flynn	University of Michigan
Richard Guy	University of California, San Francisco
Dale Hattis	Clark University
Howard Maibach	Unviersity of California, San Francisco
Ronald Wester	University of California, San Francisco

Private Sector Reviewers:

Michael Bird	Exxon Biomedical
Clay Frederick	Rohm & Haas Co.
Cindy Fuller	Woodward-Clyde Consultants
Stephen Frantz	Union Carbide
J.M. Holland	Upjohn Corp.
Bruce Houtman	Dow Elanco Co.
John Kao	Smith Kline Beecham Pharmaceuticals
Richard Nolan	Dow Chemical
Boyd Paulsen	Syntex Corp.
Timothy Roy	Mobil Oil Corp.
Tom Spencer	Cygnus Labs
Joe Yang	Mobil Oil Corp.

ACKNOWLEDGEMENTS

The document authors would like to acknowledge the contributions of the following individuals from Versar, Inc:

Wordprocessing: Valerie Schwartz, Sally Gravely, Bridgett Hamilton-Brown, Shirley Harrison, Sylvia Johnson, Susan Perry, and Chris Thompson

Spreadsheet Analysis: Robert Fares

Project Management: Greg Schweer, Gary Whitmyre

Graphics: Kathy Bowles

The authors also thank the following individuals from Technical Resources, Inc. who contributed to the preliminary drafts of this document: Louis Cofone, Isaac Divan, Abraham Mittelman and Kathleen Plourd.

Special thanks are extended to Carol Henry and Larry Fishbein at the Risk Science Institute who helped organize and conduct the review workshop.

Finally, we would like to thank Judy Theisen and Terri Konoza of EPA who conducted the final document editing.

SYMBOLS

β:	Constant used in Kasting et al. model (dimensionless)
ΔC:	Concentration gradient across a dermal barrier (mg/cm^2)
ΔH_{vap}:	Enthalpy of vaporization (cal/mol)
τ:	Lag time (hr)
ρ_{neat}:	Density of neat compound (g/cm^3)
ρ_{soil}:	Density of soil (g/cm^3)
A:	Skin surface area available for contact (cm^2)
A_t:	Total skin surface area (cm^2)
A_L:	Area fraction of the lipophilic pathway
A_P:	Area fraction of the polar pathway
ABS:	Absorption Factor (unitless)
ABS_{GI}:	Absorption factor in GI tract (unitless)
AF:	Soil-to-skin adherence factor (mg/cm^2-event)
AT:	Averaging time (days)
B:	A dimensionless constant reflecting the partitioning properties of a compound used in the Bunge model (1991)
BW:	Body weight (kg)
C:	Concentration (mg/cm^3 or mg/kg)
C_o:	Initial concentration (mg/cm^3 or mg/kg)
C_e:	Equilibrium concentration of a compound in solution after exposure to a known mass of skin (mg/cm^3)
C_{skin}:	Concentration of a compound in the skin (mg/cm^3)

C_v:	In the Kasting et al. (1987) model, the vehicle concentration, and the common practice is to measure flux as a function of this parameter and to report the ratio as the permeability coefficient
C_w:	Concentration of a compound in the water (mg/cm^3 or mg/L)
C_{os}:	Concentration of a compound in organic solvent (mg/cm^3 or mg/L)
C_{air}:	Concentration of a compound in the air (mg/cm^3)
C_{soil}:	Concentration of a compound in the soil (mg/kg)
C^o_{soil}:	Initial concentration of a compound in soil (mg/kg)
C^{sat}_m:	Saturation concentration of a chemical in a membrane (mg/cm^3)
C^{sat}_{os}:	Saturation concentration of a chemical in skin (mg/cm^3)
C^{sat}_{air}:	Saturation concentration of a chemical in air (mg/m^3)
C^{sat}_w:	Saturation concentration of a chemical in water (mg/L)
C^o_{donor}:	Initial concentration of a chemical in the donor solution as used in vitro experiments (mg/L)
C_{donor}:	Initial concentration of a chemical in the donor solution as used in in vitro experiments (mg/L)
$C^o_{receiver}$:	Initial concentration of a chemical in the receiving solution as used in in vitro experiments (mg/L)
$C_{receiver}$:	Concentration of a chemical in the receiving solution as used in in vitro experiments (mg/L)
D:	When used to determine the relationship between the rates of capillary transfer and diffusion, the average membrane diffusion coefficient
D^o:	Diffusivity constant used in Kasting et al.'s model
D_L:	Diffusivity of a substance in the lipid phase (cm^2/hr)
D_P:	Diffusivity of a substance in the protein phase (cm^2/hr)
D_m:	Diffusivity of a substance within the membrane (cm^2/hr)
D_s:	Diffusivity of a substance within the skin (cm^2/hr)

D_{sc}:	Diffusivity of a substance within the membrane (cm^2/hr)
D_{ve}:	Diffusivity of a substance within the viable epidermis (cm^2/hr)
DA_{event}:	Dose absorbed per unit area per event (mg/cm^2-event)
DA_t:	Total dose absorbed per day (mg/day)
DAD:	Daily average lifetime exposure (mg/kg-day)
ED:	Exposure duration (year)
EF:	Exposure frequency (days/year) for water exposure; (events/year) for soil exposure
EV:	Event frequency (events/day)
f:	Pathway exposure factor (age group) (L/kg-day)
f_s:	Fraction of skin exposed (unitless)
f_z:	Fugacity (Pa)
F:	Overall pathway exposure factor (L/kg-day)
H:	Henry's Constant (atm-m^3/mole)
IR:	Ingestion rate (L/day) for water; (mg/day) for soil
J_{max}:	Maximum flux (mg/cm^2-hr)
J_{ss}:	Steady-state flux, i.e., J plotted as a function of time and showing little change over time (mg/cm^2-hr)
k_{soil}:	Rate constant for disappearance of chemical from soil (hr^{-1})
k_{vol}:	Rate of volatilization from soil ($hour^{-1}$)
K_h:	Dimensionless Henry's Constant
K_D:	Partition coefficient between soil and water (L/kg)
$K_{1,2}$, $K_{2,3}$, $K_{1,3}$:	Partition coefficients between the various phases 1, 2, 3 (dimensionless)
$K_{ac/w}$:	Partition coefficient between amyl caproate and water (dimensionless)
$K_{air/w}$:	Partition coefficient between air and water (dimensionless)

$K_{b/w}$:	Partition coefficient between benzene and water (dimensionless)
$K_{e/w}$:	Partition coefficient between ether and water (dimensionless)
$K_{hex/w}$:	Partition coefficient between hexadecane and water (dimensionless)
$K_{n/w}$:	Partition coefficient between neat compound and water (dimensionless)
$K_{o/w}$:	Partition coefficient between octanol and water (dimensionless)
$K_{ol/w}$:	Partition coefficient between olive oil and water (dimensionless)
$K_{soil/w}$:	Partition coefficient between soil and water (dimensionless)
$K_{t/w}$:	Partition coefficient between tetradecane and water (dimensionless)
$K_{m/v}$:	Partition coefficient between membrane and vehicle contacting membrane (dimensionless)
$K_{m/os}$:	Partition coef[illegible]nt between membrane and organic solvent [illegible]sionless)
$K_{m/w}$:	Partition coefficient between membrane and water (dimensionless)
$K_{f/a}$:	Partition coefficient between fat and air (dimensionless)
$K_{s/air}$:	Partition coefficient between soil and air (dimensionless)
$K_{s/v}$:	Partition coefficient between soil and vehicle (dimensionless)
$K_{s/os}$:	Partition coefficient between soil and organic solvent (dimensionless)
$K_{soil/w}$:	Partition coefficient between soil and water (dimensionless)
$K_{s/soil}$:	Partition coefficient between skin and soil (dimensionless)
$K_{sc/w}$:	Partition coefficient between stratum corneum and water (dimensionless)
K_p, $K_{p,s}$:	Permeability coefficient for chemical from an unspecified vehicle through the skin (cm/hr)
K_p^{air}:	Permeability coefficient for chemical from air through the skin (cm/hr)
$K_{p,ve}^{lim}$:	Upper limit to permeability coefficient for chemical from a vehicle through the skin (cm/hr)
$K_{p,s}^{neat}$:	Permeability coefficient for a neat chemical through the skin (cm/hr)

$\mathbf{K_{p,s}^{os}}$:	Permeability coefficient for chemical from organic solvent through the skin (cm/hr)
$\mathbf{K_{p}^{soil}}$:	Permeability coefficient for a chemical in soil through the skin (cm/hr)
$\mathbf{K_{p,s}^{soil}}$:	Permeability coefficient for a chemical in soil through the skin (cm/hr)
$\mathbf{K_{p}^{vap}}$:	Permeability coefficient for a chemical in vapor through the skin (cm/hr)
$\mathbf{K_{p(est)}^{vap}}$:	Estimated permeability coefficient for a chemical in vapor through the sk (cm/hr)
$\mathbf{K_{p}^{w}}$:	Permeability coefficient for chemical from water through the skin (cm/hr)
$\mathbf{K_{p,s}^{w}}$:	Permeability coefficient for chemical from water through the skin (cm/hr)
$\mathbf{K_{p(exp)}^{w}}$:	Experimental permeability coefficient for chemical from water through t skin (cm/hr)
$\mathbf{K_{p(est)}^{w}}$:	Estimated permeability coefficient for a chemical in water through the sk (cm/hr)
$\mathbf{l_{m}}$:	Membrane thickness (μm)
$\mathbf{l_{s}}$:	Skin thickness (μm)
$\mathbf{l_{sc}}$:	Thickness of stratum corneum (μm)
$\mathbf{l_{ve}}$:	Thickness of viable epidermis (μm)
M:	Amount absorbed per event (mg/event)
MP:	Melting point (°C or °K)
$\mathbf{MR_{d}}$:	Molar refractivity
MV:	Molar volume
MW:	Molecular weight (g/gmole)
$\mathbf{MW_{a}, MW_{b}}$:	The molecular weight of a structurally analogous compound (g/gmole)
$\mathbf{P_{a}, P_{b}}$:	Actual pressure (atm or mm Hg)
$\mathbf{P^{sat}}$:	Saturation pressure (atm or mm Hg)
$\mathbf{P_{a}^{vap}, P_{b}^{vap}}$:	Vapor Pressure (atm or mm Hg)

q^*:	95% upper-confidence limit of the linear-slope factor (kg-day/mg)
R:	Universal gas constant = 8.205×10^{-5} m^3-atm/mole°K
RfD:	Reference Dose (mg/kg-day)
S:	Molar solubility in water (mole/L H_2O)
T_a,T_b:	Temperature (°C or °K)
t_{event}:	Event time (hr/event)
V_{donor}:	Volume of donor solution used in in vitro experiments (cm^3)
$V_{receiver}$:	Volume of receiver solution used in in vitro experiments (cm^3)
V_{sc}:	Volume of stratum corneum (cm^3)
V_w:	Volume of water, the aqueous phase (cm^3)
Z:	Fugacity capacity (mol/m^3 - Pa)
Z_{air}:	Fugacity capacity of air (mol/m^3 - Pa)
Z_{water}:	Fugacity capacity of water (mol/m^3 - Pa)
Z_{soil}:	Fugacity capacity of soil (mol/m^3 - Pa)

1. INTRODUCTION

The goal of this document is to provide exposure assessors with an understanding of the principles of dermal absorption and the procedures for applying these principles to human exposure situations. More specifically, this document:

- Summarizes the current state of knowledge concerning dermal exposure to water, soil, and vapor media;
- Presents methods for estimating dermal absorption resulting from contact with these media and elaborates upon their associated uncertainties;
- Summarizes available chemical-specific experimental data describing the dermal absorption properties and provides predictive techniques to use where data are not available; and
- Establishes a procedure for evaluating experimental data for application to exposure assessments.

The scope of this document focuses primarily on the needs of exposure assessors evaluating waste disposal sites or contaminated soils. Such sites can have releases to the air and water. Accordingly, the dermal contact pathways specifically addressed are direct contact with soils, contact with contaminants in water, and contact with vapors. Obviously, other dermal contact pathways of concern can occur. Most notable, perhaps, is direct contact with commercial products. Waste sites usually involve relatively low contaminant concentrations and generally pose chronic rather than acute health hazards. Thus, priority was given to developing procedures oriented toward chronic risks rather than acute risks. Chronic effects can be manifested inside the body (i.e., systemically) or in the skin itself (i.e., point of entry effects). An additional scoping decision was made to focus on procedures oriented toward systemic effects. The decisions to limit the scope orientation to chronic systemic effects is supported by the fact that Agency exposure/risk assessors rely largely on the dose-response data provided in the Integrated Risk Information System (IRIS). This database currently contains only chronic ingestion and inhalation dose-response data, and thus cannot be used to assess acute and/or direct skin effects. (The uncertainties associated with this procedure are discussed in more detail in Chapter 10). In spite of these limitations in scope, much of the material in this document is generic in nature, and should prove helpful to individuals with interests outside this scope. Figure 1-1 illustrates how the dermal exposure and risk assessment processes vary according to the type of health effects of concern and identifies the path given highest priority in this document.

Exposure is defined as the contact between a contaminant and the external boundary of an organism. However, exposure assessors traditionally estimate the quantities needed to evaluate risk, and, as a result, may go beyond the strict definition of exposure to an estimate of dose. Such dose estimates are clearly needed in dermal exposure assessments oriented toward chronic systemic effects. Thus, dermal exposure assessment is defined here as including the estimation of absorbed dose from contaminants contacting the skin.

This document is divided into two parts. Part 1 consists of Chapters 2 through 7 and describes general principles of dermal absorption. Part 2 encompasses the remainder of the document and presents methods for applying the principles described in Part 1 to human exposure assessments. Each chapter is summarized briefly below:

PART 1. PRINCIPLES

Chapter 2	Describes the biological mechanisms of dermal absorption, i.e., amount of contaminant that crosses the skin and enters the body; includes discussion of skin structure, transport processes, metabolism, and factors that influence dermal absorption such as body site and hydration level. This chapter establishes the theoretical basis for absorption issues presented in Chapters 4 through 7.
Chapter 3	Describes laboratory techniques for measuring dermal absorption. It includes a number of in vivo and in vitro methods and comparisons of these methods.
Chapter 4	Describes mathematical procedures for estimating dermal absorption.
Chapter 5	Addresses dermal uptake of chemicals in water, summarizing both experimental data and estimation procedures.
Chapter 6	Addresses dermal uptake of chemicals in soil, summarizing both experimental data and estimation procedures.
Chapter 7	Addresses dermal uptake of chemicals in air, summarizing both experimental data and estimation procedures.

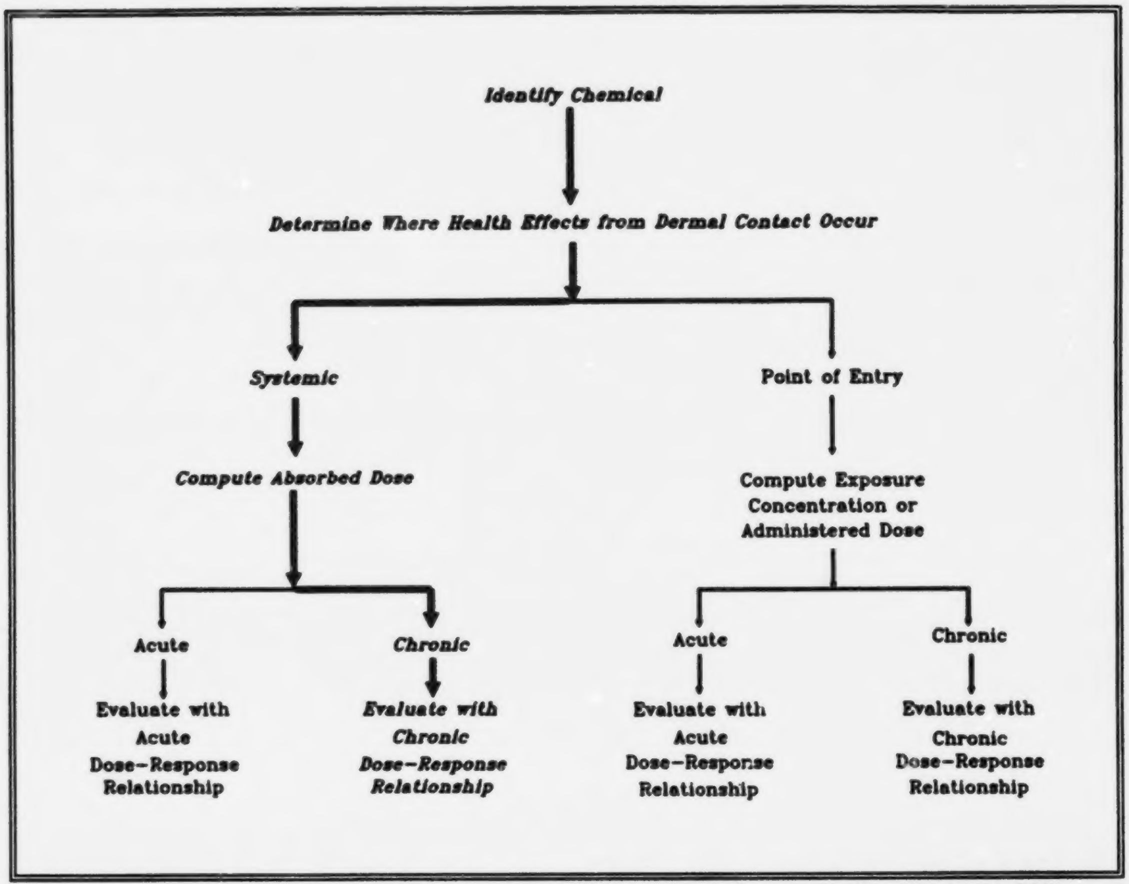
Identify Chemical
Determine Where Health Effects from Dermal Contact Occur
Systemic
Point of Entry
Compute Absorbed Dose
Compute Exposure Concentration or Administered Dose
Acute
Chronic
Acute
Chronic
Evaluate with Acute Dose-Response Relationship
Evaluate with Chronic Dose-Response Relationship
Evaluate with Acute Dose-Response Relationship
Evaluate with Chronic Dose-Response Relationship

Figure 1-1. Dermal risk assessment process. Bolded arrows show procedure covered within the scope of this document.

PART 2. APPLICATIONS

Chapter 8	Presents methods for characterizing dermal exposure scenarios. Includes discussion of area of exposed skin, contact duration and frequency, body surface area, and soil adherence.
Chapter 9	Offers exposure/risk assessors guidance to determine when dermal exposure will contribute significantly to total absorbed dose. It presents existing literature comparing routes of exposure as proportion of total dose for aqueous media, soil, and vapors.
Chapter 10	Describes a step-by-step procedure to conduct a dermal exposure assessment. Default assumptions are included for situations where information is not available.

Finally, the exposure/risk assessor should be cautioned that this area remains the least well understood of the major exposure routes (i.e., ingestion, inhalation, and dermal contact). Very little chemical-specific data are available, especially for soils, and the predictive techniques have not been well validated. Furthermore, dose-response relationships specific to dermal contact are not commonly available. Accordingly, considerable uncertainty surrounds estimates of dermal exposure/risk, and careful judgement should be used to interpret these results.

PART 1. PRINCIPLES OF DERMAL EXPOSURE ASSESSMENT

2. MECHANISMS OF DERMAL ABSORPTION

The skin is a highly organized, heterogeneous, and multilayered organ. The sum total of the various layers forming the epidermis and dermis, together with its appendages and underlying microvasculature, constitute a living envelope surrounding the body. Until recently, skin absorption studies focused to a great extent on physico-chemical and biophysical factors. However, recent discoveries in the immunological and metabolic capacities of the skin have expanded our appreciation of the functional and biochemical versatilities of this complex organ. In addition to producing mediators of inflammatory and immune responses, the skin produces factors that regulate growth and differentiation. These factors make the skin more than an inert barrier and it should be viewed as a dynamic, living tissue whose permeability characteristics are susceptible to change. Therefore, there are abundant biochemical and physiologic factors that remain to be systematically investigated.

The permeability coefficient (K_p) is a key parameter in estimating dermal absorption. The effective use of K_p values in dermal exposure assessments requires understanding of the processes that affect the transport of compounds across the skin. An understanding of these processes will enable the exposure/risk assessor to evaluate the appropriateness of using the available K_p values to estimate dermally absorbed dose in site- or scenario-specific exposure/risk assessments. In this chapter, the mechanisms by which compounds are absorbed (or removed) from the skin are explored, and factors that affect this absorption process are considered. This chapter shows how the exposure/risk assessor can use this information to make the qualitative judgements about the appropriateness of K_p values generated in a study with a defined set of conditions that may be different from those encountered in the exposure scenario of interest.

2.1. STRUCTURE AND FUNCTION OF THE SKIN

The general anatomy and morphology of the skin have been well characterized. Several detailed reviews of the physical nature of the skin are available (e.g., Marks et al., 1988; Elias et al., 1987), and the reader is directed to these reviews for a thorough discussion of this topic. However, percutaneous absorption is highly influenced by the microstructure and biochemical composition of the skin. Therefore, a brief review is presented in this chapter to better allow the exposure/risk assessor to interpret compound-specific dermal absorption rate data relative to the structure of the skin.

The skin is composed of two layers: the epidermis, a nonvascular layer about 100 μm thick, and the dermis, a highly vascularized layer about 500 to 3,000 μm thick. The outermost layer of the epidermis, the stratum corneum is about 10-40 μm thick. This layer is thought to provide the major barrier to the absorption into the circulation of most substances deposited on the skin surface. It is composed of dead, partially desiccated, and keratinized epidermal cells. Below this layer lies the viable epidermis, a region about 50-100 μm thick, containing at its base the germinative or basal cell layer whose cells move outward to replace the outer epidermis as it wears away. This layer generates about one new cell layer per day, which results in the stratum corneum becoming totally replaced once every two to three weeks. The viable epidermis contains enzymes that metabolize certain penetrant substances. Enzymes may also be active in the stratum corneum (Marzulli et al., 1969), if cofactors are not required.

Below the epidermis lies the dermis, a collagenous, hydrous tissue. The hair follicles and sweat ducts (skin appendages) originate deep within the dermis and terminate at the external surface of the epidermis. These occupy only about 1% of the total skin surface, and therefore their role as transport channels for the passage of substances from the external environment to the capillary bed is thought to be negligible for most chemicals (Scheuplein and Blank, 1971). The structure of the skin is shown diagrammatically in Figure 2-1.

As mentioned above, the stratum corneum is generally considered to be the rate-limiting diffusion barrier for most compounds. Because of the importance of this layer in determining the rate and extent of dermal absorption, the following discussion will focus on its structure and function.

Michaels et al. (1975) described the stratum corneum as a heterogeneous structure containing about 40% protein (primarily keratin), 15% to 20% lipids, and 40% water. Lipids in the stratum corneum exist principally in the form of triglycerides, fatty acids, cholesterol, and phospholipids. Michaels et al. (1975) conceptualized the stratum corneum as being composed of parallel arrays of proteinaceous cells separated by thin layers of lipoidal material in a "bricks and mortar" arrangement (Figure 2-2).

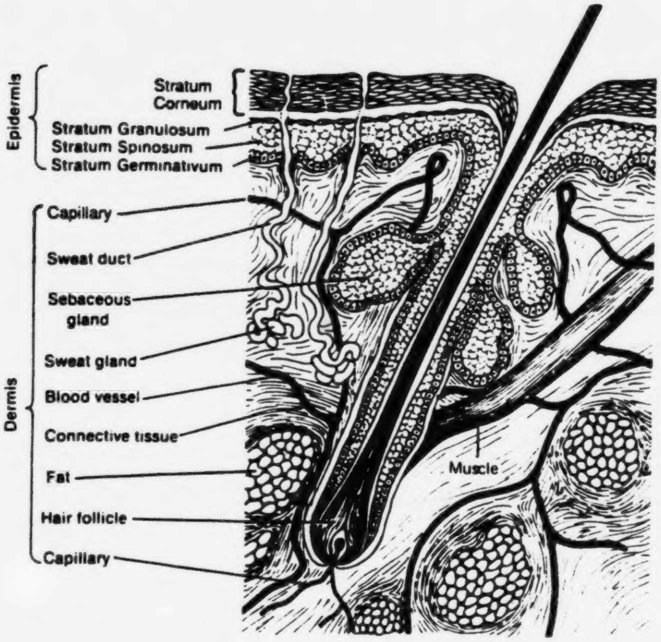
Epidermis
Stratum Corneum
Stratum Granulosum
Stratum Spinosum
Stratum Germinativum
Capillary
Sweat duct
Sebaceous gland
Sweat gland
Blood vessel
Dermis
Connective tissue
Fat
Hair follicle
Capillary
Muscle

Figure 2-1. Structure of the skin.

Source: Casarett and Doull (1986)

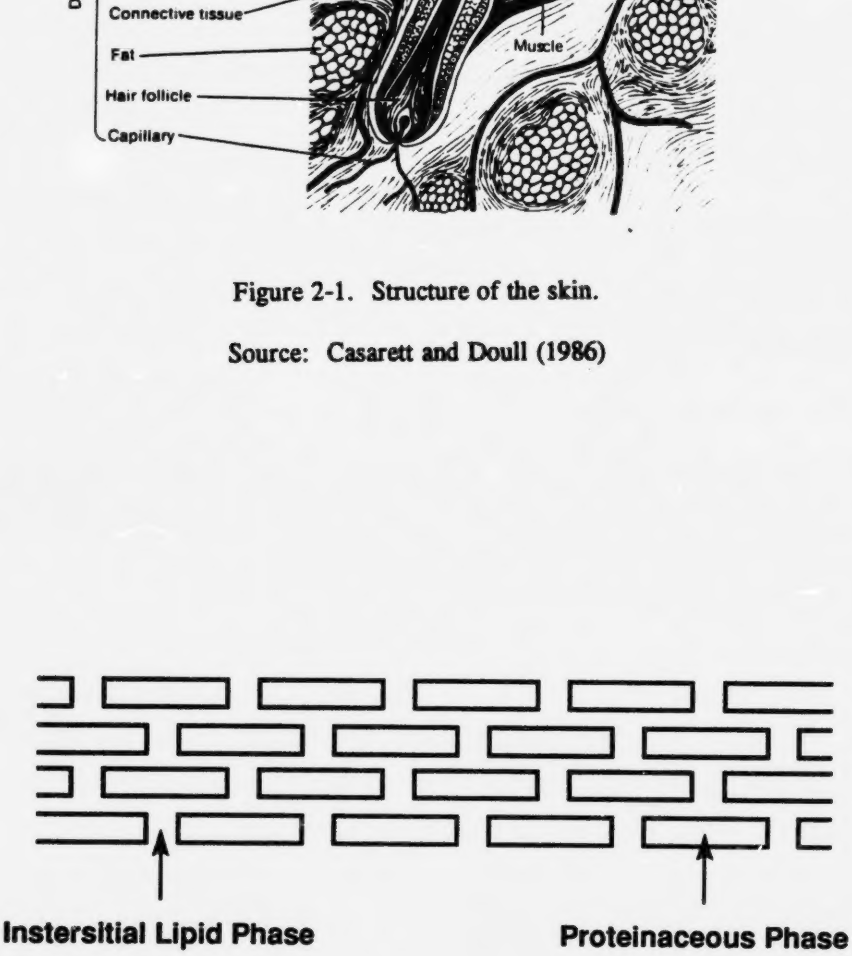
Instersitial Lipid Phase
Proteinaceous Phase

Figure 2-2. Two-phase model of the stratum corneum.

Source: Michaels et al. (1975)

Raykar et al. (1988) reported that the lipid content of dry stratum corneum in 35 human skin samples ranged from 3% to 46% depending on skin site and the individual. Using a factor of 4 to convert dry to hydrated stratum corneum, the range is 1% to 11%. This wide range is important with regard to the role of lipophilicity in storage, membrane functions, and skin site.

As outlined in Table 2-1, evidence for this two-phase (lipid and protein) model comes from permeation, freeze-fracture, histochemical, biochemical, and x-ray diffraction studies.

Table 2-1. Evidence for the Two-Phase Model of the Stratum Corneum

- Physico-chemical evidence for two pathways of transport of lipid and water-soluble molecules
- Freeze-fracture morphology
- Histochemistry and fluorescence staining of lipids in frozen sections
- Dispersion by lipid solvents
- Co-localization of lipid catabolic enzymes
- Membrane isolation and characterization, including x-ray diffraction

Source: Elias et al. (1987)

Evidence for this two-phase system, based on the physico-chemical properties of permeable compounds, was offered by Raykar et al. (1988). These researchers reported that solutes with octanol/water partition coefficients less than 1,000 had similar partition coefficients for whole stratum corneum/water and delipidized stratum corneum/water. This finding suggests that these compounds were taken up largely or entirely by the protein domain in the stratum corneum. Conversely, for lipophilic compounds (octanol/water partition coefficient greater than 1,000) an increasing divergence between whole stratum corneum/water and delipidized stratum corneum/water partition coefficient values was observed with increasing lipophilicity.

Freeze-fracture and x-ray diffraction studies have demonstrated that the lipid in the stratum corneum is limited to the interstitial areas; no lipid is found in the cytosol of the keratinized cells. Lipids have also been identified as being localized to the intercellular areas by histochemical staining.

Lipid solvents easily disperse the stratum corneum into a cellular suspension, thereby lending support for a lipid-rich intercellular area.

2.2. FATE OF COMPOUNDS APPLIED TO THE SKIN

Numerous environmental pollutants are known to permeate the skin's diffusional barriers and enter the systemic circulation via capillaries at the dermo-epidermal junction. Thus, percutaneous absorption can be regarded as the translocation of skin surface-applied chemicals through the various strata of the epidermis and a small portion of underlying dermis that contains papillary capillaries, outposts of the systemic circulation, where penetrating substances are first delivered to the blood stream (Figure 2-1). This is a process that begins with diffusion through the dead stratum corneum and may involve metabolic processes during traversal of the living epidermis. The fates of compounds that come into contact with skin are summarized in Figure 2-3 as follows:

- Evaporation from the surface of the skin;
- Uptake (sorption) into the stratum corneum, followed by reversible or irreversible binding; or
- Penetration into the viable epidermis, followed by metabolism.

In many of the studies used to generate the K_p values, the extent of skin absorption was estimated by measuring the loss of compound from the skin surface. However, if loss processes, such as those presented in Figure 2-3, are occurring, an overestimation of the extent and rate of skin absorption may be made. Therefore, this section reviews not only the processes by which compounds are absorbed across the skin, but other loss processes as well, to enable the exposure/risk assessor to effectively use the K_p values.

2.2.1. Transport Processes Occurring in the Skin

The two-phase structure of the stratum corneum suggested by the studies reviewed in the previous section has a marked effect on the permeation of compounds through this diffusional barrier. Penetrant molecules can follow an intercellular or transcellular route through the stratum corneum, as shown in Figure 2-4, depending on their relative solubility and partitioning in each phase.

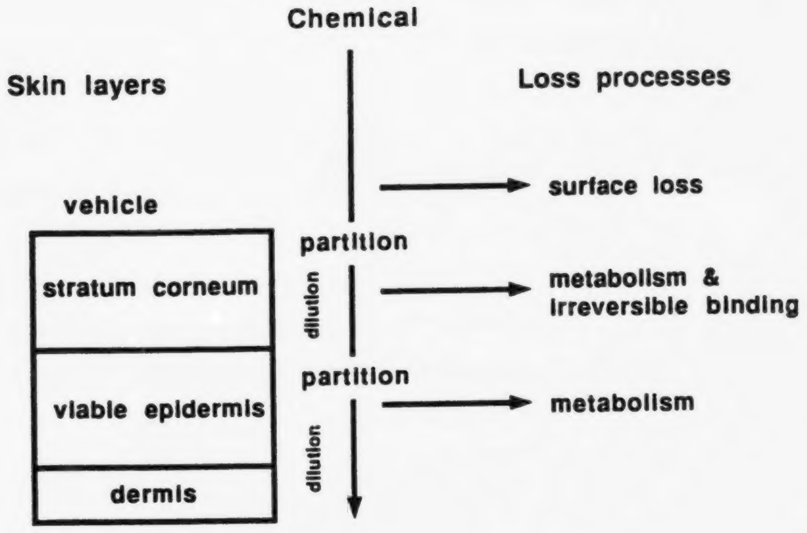
Chemical
Skin layers
Loss processes
vehicle
surface loss
partition
stratum corneum
dilution
metabolism &
irreversible binding
partition
viable epidermis
metabolism
dilution
dermis

Figure 2-3. Transport/loss processes occurring in the skin.
Source: Adapted from Guy and Hadgraft (1989a)

Evidence for the existence of separate pathways for hydrophilic and lipophilic molecules was offered by Michaels et al. (1975). These investigators reported that when a penetrant exists in both nonionic and ionic forms, the nonionic (and therefore more lipophilic) form is the better skin penetrant. Flynn (1985) made the same argument after considering the total literature.

An alternative to transport of a compound through transcellular or intercellular pathways in the stratum corneum, shown in Figure 2-3, is penetration via skin appendages, such as hair follicles, sebaceous glands, and sweat glands. These appendages could serve as diffusional shunts through rate-limiting barriers, thereby facilitating the skin absorption of topically applied chemicals. However, since they occupy less than 1% of the skin surface for humans, their role as transport channels for the passage of substances from the external environment to the capillary bed is often negligible.

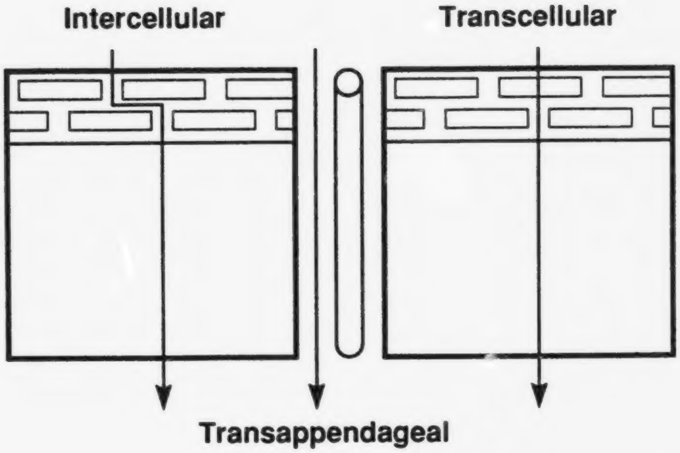

Figure 2-4. Major routes of diffusion through the skin.
Source: Guy and Hadgraft (1989a)

Nevertheless, for slowly diffusing chemicals, transappendageal absorption may be a contributing or even dominant pathway of dermal permeation, especially during the period immediately following application of the compound to the skin (Blank and Scheuplein, 1969). For example, the high follicular density of the scalp may enhance the follicular absorption route during swimming. Using a lipophilic compound (benzo[a]pyrene) and a more polar compound (testosterone), Kao et al. (1988) recently examined the extent to which the transappendageal route contributes to the dermal absorption of these compounds. For the lipophilic benzo[a]pyrene, the rate and degree of skin permeation in mice was significantly greater in the haired strain (Balbc) than in the hairless strain (SKH). Conversely, there was little difference in the in vitro skin permeation of topically applied testosterone between haired and hairless strains of mice. Hairless animals, however, tend to have a better developed stratum corneum than haired species and strains within a species. Appendageal penetration was also discussed by Tregear (1966) and by Guy and Hadgraft (1984). Although the mice were genetically related, other differences in skin structure cannot be ruled out to account for the observed differences in percutaneous absorption.

2.2.2. Loss Processes Occurring in the Skin

As mentioned above, a compound coming into contact with the skin cannot only cross the diffusional barrier and be taken up by the capillary network for systemic circulation, but also can evaporate from the surface of the skin, bind to stratum corneum, penetrate into stratum corneum, or become metabolized. These processes are described below.

2.2.2.1. *Evaporation from the Surface of the Skin*

Reifenrath and Spencer (1989) reviewed the processes that play a role in the evaporation of compounds from the skin. These include wind, humidity, temperature, and vapor pressure. Processes that lead to increased volatilization of the compound on the skin surface (high wind speed and temperature, low humidity) will accelerate the loss of compound from the skin by evaporation and reduce the dose available for absorption. The role of vapor pressure on the disposition of a topically applied compound is demonstrated in Table 2-2. Hawkins and Reifenrath (1984) showed that evaporation accounted for only 4% of the applied radioactive dose of DDT, a relatively nonvolatile compound applied to pig skin in vitro, but is responsible for the loss of 65% of a volatile compound such as diisopropyl fluorophosphonate. Despite their loss by evaporation from the skin surface, volatile compounds tend to be good skin penetrants.

Percutaneous absorption studies are often conducted by covering the site of application with an occlusive wrap to protect the site or prevent loss of the compound. Application of occlusive wrap will limit the evaporation of volatile compounds from the surface of the skin, and may, therefore, increase the extent or rate of percutaneous absorption of these compounds. For example, Bronaugh et al. (1985) demonstrated that the percutaneous absorption of a single dose of volatile fragrance compounds in monkeys was increased after occlusion of the application site with plastic wrap. However, occlusion of the site also increases the hydration of the stratum corneum, which may also be responsible for the increased absorption seen in this study. The effect of occlusion on percutaneous absorption has been discussed by Bucks et al. (1991).

Table 2-2. Comparison of Vapor Pressure and Disposition of Radioactivity After Topical Application of Radiolabeled Control Compounds to Pig Skin Under Standardized Conditions

Compound	Vapor Pressure (mm Hg at 20°C)	Evaporation Loss; Percent of Applied Radioactive Dose
DDT	1.5×10^{-7}	4 ± 5
Parathion	4.7×10^{-6}	7 ± 0.6
Malathion	5.5×10^{-6}	17 ± 6
Lindane	3.3×10^{-5}	26 ± 5
Benzoic acid	3.8×10^{-4}	5.7 ± 0.3
N,N-Diethyl-*m*-toluamide	1.03×10^{-3}	21 ± 6
Diethyl malonate	2.49×10^{-1}	40 ± 10
Diisopropyl fluorophosphonate	5.79×10^{-1}	65 ± 8

Source: Hawkins and Reifenrath (1984)

Because of the potential for evaporation from the skin to affect the rate and extent of percutaneous absorption, the exposure/risk assessor is advised to take this factor into consideration when using the K_p values in calculations of dermally absorbed dose in specific exposure scenarios. Although this factor is perhaps most important to consider when assessing the absorption of a neat compound applied to the skin, volatile compounds in aqueous solution or a soil medium will also evaporate from those vehicles. The complexity of this problem is demonstrated by findings of Moody et al. (1987) that show enhanced persistence of Fenitrothion on skin where insect repellent N, N-diethyl-*m*-toluamide (DEET) was applied. This effect could have exposure consequences to workers who are occupationally exposed to both compounds.

2.2.2.2. *Binding of Compounds in the Skin*

Compounds can be retained in the skin, to some degree, by temporarily partitioning into the protein or lipid phases of the various dermal strata. Compounds can also be retained in the skin by virtue of either reversible or irreversible binding to skin tissue. As shown in Figure 2-3, irreversible binding and eventual sloughing of the cells in the stratum corneum may limit the percutaneous absorption of a compound.

Binding of a compound may also occur in the epidermal or dermal/skin layers. Such binding and the establishment of a reservoir of the compound in the skin could result in the creation of a pharmacokinetic compartment with a slow turnover rate.

Wester et al. (1987) recently used compound binding to the stratum corneum as a means to evaluate the total skin absorption of environmental chemical contaminants in ground and surface water. Using the assumption that any chemicals bound to the skin will be ultimately absorbed into the body, these investigators underscored the importance of percutaneous absorption as a route of exposure to environmental pollutants during swimming or bathing.

2.2.2.3. *Metabolism*

Metabolism is an important factor in determining both the rate and amount of percutaneous absorption. The metabolic activity of the epidermis, in turn, depends on the distribution and activity of specific enzyme systems and on the rate of chemical diffusion.

As shown in Figure 2-3, metabolism may influence the bioavailability of topically applied compounds. The skin may act as a site of "first pass" metabolism serving, in most cases, to assist in chemical detoxification. For example, in vitro studies involving topically applied benzo[a]pyrene (BaP) and testosterone to viable skin of human, mouse, rat, guinea pig, rabbit, and marmoset (skin) were carried out by Kao et al. (1985) to demonstrate the importance of metabolic processes. Moreover, it has been shown (Kao et al., 1984) that enzyme induction, via pretreatment in vivo with TCDD, affects cutaneous metabolism in vitro following treatment with lipophilic compounds such as BaP. A recent study by Thohan et al. (1989) in the rat demonstrated that pretreatment with Arochlor 1254 administered intraperitoneally results in a greater degree of 7-ethoxycoumarin diethylase induction in skin microsomes than in hepatic microsomes.

In their review of cutaneous xenobiotic metabolism, Noonan and Wester (1989) strongly argued for greater emphasis on metabolic activity versus sole reliance on passive diffusion processes. According to their thesis, the lipid-saturated stratum corneum, the primary diffusional barrier, acts as a sink for lipophilic compounds such as BaP and steroids. The metabolic activity of the viable epidermis may then be the rate-limiting factor affecting delivery of the compound to the vasculature in the dermis. While it is often assumed that skin metabolic rates are significantly lower than hepatic rates, the activity ratio of epidermis (primary cutaneous metabolic site) to liver is comparable for certain enzymes such as aromatic hydrocarbon hydroxylase (AHH), 7-ethoxycoumarin diethylase, aniline hydroxylase, and NADP-cytochrome c reductase (Noonan and Wester, 1989). Such activity comparisons may be misleading, however, unless they take into account heterogeneity in enzyme distribution.

Numerous studies have been carried out demonstrating cutaneous metabolism of polycyclic aromatic hydrocarbons (PAHs). Incubation of BaP with human epithelial cell culture has yielded metabolites such as 3- and 9-hydroxy-benzo[a]pyrene, 7,8- and 9,10-dihydrodiol derivatives, and 1,6-, 6,12- and 3,6-quinone derivatives (Fox et al., 1975). While Pohl et al. (1976) determined the AHH activity to BaP in whole skin to be 2% of that in the liver, Noonan and Wester (as mentioned above) estimated the epidermal AHH activity as 80% relative to the liver, a far more significant contribution even assuming variation in enzyme distribution. This assumes that all activity is in epidermis, and that epidermis is 2.5% by weight of whole skin.

Skin has also been shown to contain PAH detoxification enzyme systems. Bentley et al. (1976) identified the presence of epoxide hydrase in rat skin, an enzyme involved in the detoxification of BaP epoxides via conversion to their corresponding dihydrodiols. Skin tissues also contain conjugating enzyme systems capable of enhancing elimination of compounds such as BaP. Glucuronidation of hydroxylated BaP has been reported by Harper and Calcutt (1960). While sulfate conjugation of certain steroids has been reported (Berliner et al., 1968; Faredin et al., 1968), similar sulfate conjugation for PAHs has not yet been shown to occur.

Other detoxification systems such as hydrolytic esterases have been found in epidermal tissue. Chellquist and Reifenrath (1988) evaluated the in vitro distribution and fate of diethyl malonate using both normal and heat-treated pig skin. Nearly complete hydrolysis of diethyl malonate occurred in normal tissue. Human, guinea pig, and rat skin also contain such hydrolytic esterases. Diflucortolone valerate (DFV) was rapidly hydrolyzed in vitro using guinea pig or rat skin ($t_{1/2}$ = 30-60 minutes), but it was slowly hydrolyzed using human skin (5-15% metabolism in 7 hours). Esterases seem to be primarily concentrated in the epidermal layer of the skin.

Tauber and Rost (1987) reported that esterase activity for the hydrolysis of steroids esterified at the 21 position is 20-fold greater per unit volume in the epidermis than in the dermis. However, due to the greater overall mass of the dermal layer, total ester hydrolysis is approximately the same in the epidermal and dermal tissues. On the other hand, only a small portion of the dermis is involved in percutaneous absorption except when absorptive capacity of papillary capillaries of the dermis are overwhelmed by rapid transport of the penetrant (see Figure 2-1).

Deamination and dealkylation reactions in skin have also been reported. Hakanson and Moller (1963) incubated norepinephrine with rat, rabbit, mouse, and human skin. They demonstrated the availability of monoamine oxidase by identifying the deaminated metabolite dehydroxymandelic acid. Similarly, Pohl et al. (1976) identified the presence of mixed-function oxidase dealkylating activity for deethylation of 7-ethoxycoumarin in mouse skin.

Cutaneous acetylation reactions have also been demonstrated in hamster skin (Kawakubo et al., 1988). A high correlation of N-acetylation activity was observed between skin and liver for metabolism of 2-aminofluorene (2-AF) and *p*-aminobenzoic acid (PABA). The importance of such metabolic activity in the skin is underscored by the role of N-acetylation in activation of carcinogenic arylamines. Acetylating enzymes in the skin have also been shown to reduce azo bonds during in vitro percutaneous penetration studies (Collier et al., 1989a).

A method for maintaining viability of skin in diffusion cells for studying metabolism in conjunction with percutaneous absorption was published by Collier et al. (1989b). Using this method, the skin absorption/metabolism of numerous compounds has been studied (Bronaugh et al., 1989; Storm et al., 1990; Nathan et al., 1990). Approximately 5% of absorbed butylated hydroxytoluene (BHT) and acetyl ethyl tetramethyltetralin (AETT) were metabolized while no detectable metabolism of caffeine, DDT, and salicylic acid was seen in hairless guinea pig skin (Bronaugh et al., 1989). Only small amounts of absorbed BaP and 7-ethoxycoumarin were found to be metabolized in rat, fuzzy rat, hairless guinea pig, mouse, and human skin (Storm et al., 1990). However, PABA and benzocaine were extensively acetylated on the primary amino group during percutaneous absorption in the hairless guinea pig and human (Nathan et al., 1990).

Processes such as pathway-specific transport through the stratum corneum, evaporation from the surface of the skin, binding in the stratum corneum, and metabolism in the epidermis all affect the extent to which compounds are absorbed by the skin, as well as the rate of percutaneous absorption. These processes have been discussed in Section 2.2.2. as factors that can result in loss of compound from the surface of the skin. However, there are numerous other factors that the exposure/risk assessor should be aware of that affect the process of percutaneous absorption. These additional factors are addressed in Section 2.3.

2.3. FACTORS THAT INFLUENCE PERCUTANEOUS ABSORPTION

Our understanding of skin absorption is largely derived from in vivo and in vitro experiments. The rate and amount of percutaneous absorption of a compound depend highly on both the physiologic characteristics of the skin and the physico-chemical nature of the compound that comes into contact with the skin. This section reviews how skin-specific factors (e.g., skin thickness, hydration, and temperature) and compound-specific factors (e.g., lipophilicity, polarity, volatility, and solubility) are involved in determining the rate and amount of absorption by the cutaneous route.

2.3.1. Skin-Specific Factors

The use and evaluation of K_p values require the exposure/risk assessor to know the conditions under which the results were obtained. As discussed below, a number of factors (e.g., species, gender, age, site of application, and the condition of the skin, i.e., degree of hydration and temperature) can have a marked effect on the extent and rate of percutaneous absorption.

2.3.1.1. *Site of Application or Exposure*

A common assumption used in dermal exposure assessment is that K_p and percent absorbed values obtained from one site of application on the body are appropriate for all skin areas where percutaneous absorption may occur. However, as reported by Feldmann and Maibach (1967), and shown in Figure 2-5, the extent of absorption of a compound such as hydrocortisone in humans is dependent on the anatomical site to which the compound is applied.

Feldmann and Maibach later extended their investigation to include pesticides (Maibach et al., 1971). As shown in Table 2-3, a marked variation exists in the dose of parathion and malathion absorbed at different anatomical sites in humans.

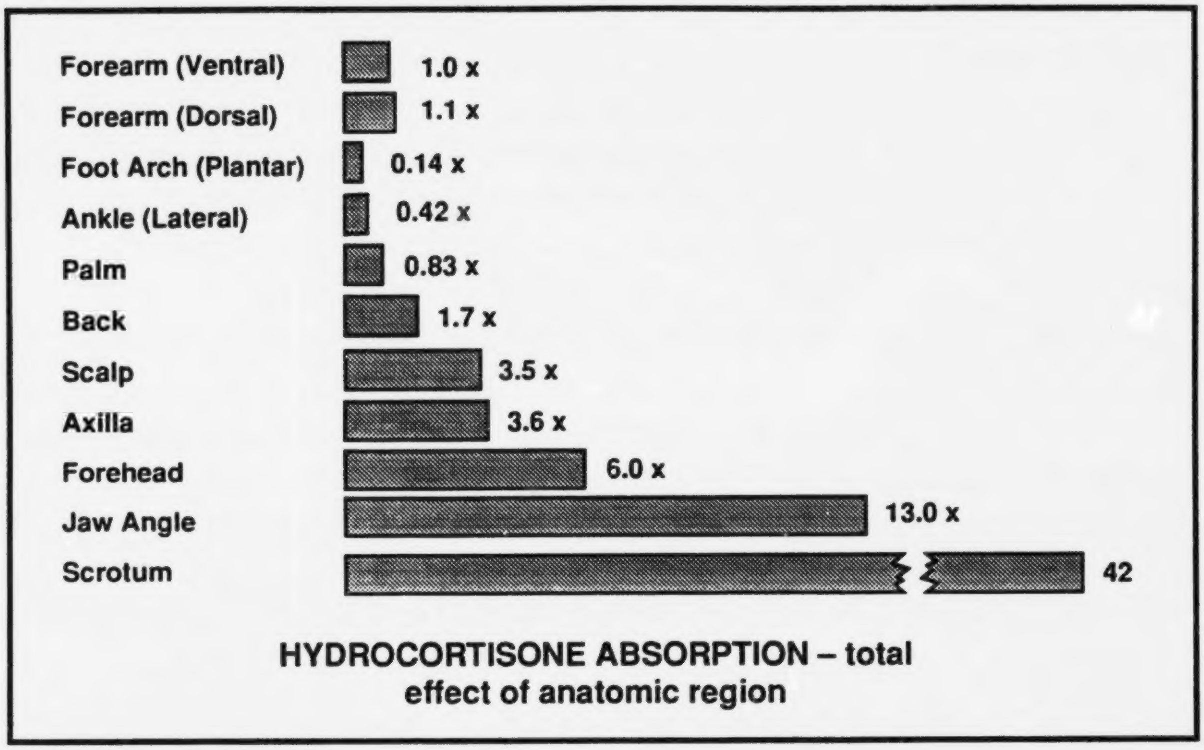

Figure 2-5. Regional variation in the percutaneous absorption of hydrocortisone in humans.

Source: Feldmann and Maibach (1967)

While the data of Table 2-3 show that human palm and forearm skin are of comparable resistance to skin penetration by parathion and malathion, in vivo, data with another compound (tri-*n*-butylphosphate) suggest that plantar skin is considerably more protective than anterior forearm when tested in vitro with this more hydrophilic compound (Marzulli, 1962). (Palmar and plantar skin are thought to be alike in physico-chemical and structural makeup.) Marzulli (1962) compared the skin permeabilities of scrotum, post auricular, scalp, thigh, instep, anterior forearm, plantar, chest, abdomen, ankle, leg, and nail which showed that the effects of regional variation appear to be modified by the type of compound involved (hydrophilic or lipophilic).

Table 2-3. Effect of Anatomical Region on In Vivo Percutaneous Absorption of Pesticides in Humans

Anatomical Region	Parathion Dose Absorbed (Percent)	Malathion Dose Absorbed (Percent)
Forearm	8.6	6.8
Palm	11.8	5.8
Foot, ball	13.5	6.8
Abdomen	18.5	9.4
Hand, dorsum	21.0	12.5
Forehead	36.3	23.2
Axilla	64.0	28.7
Jaw angle	33.9	69.9
Fossa cubitalis	28.4	
Scalp	32.1	
Ear canal	46.6	
Scrotum	101.6	

Source: Maibach et al. (1971)

Many of the K_p values come from studies using experimental animals. As expected, the percutaneous absorption of compounds also demonstrates regional variation in experimental animal species. Franklin et al. (1989) have shown that the absorption of a series of pesticides applied to the foreheads of rhesus monkeys was approximately twice that observed when the compound was applied to the forearms of these animals, as shown in Table 2-4.

Table 2-4. Percutaneous Absorption in Monkeys as Related to Site of Application and Test Compound

Compound	Forehead Percent Dose Absorbed (Percent ± SD)	Forearm Percent Dose Absorbed (Percent ± SD)
Aminocarb	74 ± 4	37 ± 14
Azinphosmethyl	47 ± 10	32 ± 9
Diethyl toluamide	33 ± 11	14 ± 5
Fenitrothion	49 ± 4	21 ± 10
Cis-permethrin	28 ± 6	9 ± 3
Trans-permethrin	21 ± 3	12 ± 3

Source: Franklin et al. (1989)

Variations in percutaneous absorption between different body sites have been reported in the rat, a commonly used species in percutaneous absorption studies. For example, Bronaugh et al. (1983) have shown that differences in the permeability of rat skin may be related not only to body site, but also to the sex of the animal. Differences have been observed in the measured permeability constants for water, urea, and cortisone across the excised male and female rat skin taken from the back of the animals, and between permeability constants measured using abdominal and back skin from male rats (Table 2-5). However, body site differences in skin permeability are not always observed for some species. For example, Behl et al. (1983b) found relatively little difference in permeability coefficients of methanol obtained using abdominal or dorsal skin from the hairless mouse.

Table 2-5. Effect of Gender and Body Site on the Permeability of Rat Skin

	Male			Female		
	Permeability Constant (cm/hr ± SD)	Lag Time (hr ± SD)	No. of Determinations	Permeability Constant (cm/hr ± SD)	Lag Time (hr ± SD)	No. of Determinations
Water						
Back	0.00049 ± 0.00004	2.4 ± 0.1	7	0.00093 ± 0.00011	2.0 ± 0.1	4
Abdomen	0.00131 ± 0.00021	1.7 ± 0.2	4			
Urea						
Back	0.00016 ± 0.00005	15.0 ± 1.8	6	0.00048 ± 0.00013	11.1 ± 0.6	3
Abdomen	0.00188 ± 0.00055	16.5 ± 4.3	4			
Cortisone						
Back	0.00017 ± 0.00004	33.4 ± 4.4	8	0.00047 ± 0.00011	20.0 ± 2.6	3
Abdomen	0.00122 ± 0.00006	32.9 ± 2.4	4			

Source: Bronaugh et al. (1983)

Although gender-related permeability differences have not been measured directly in humans, animal data that demonstrate gender differences are frequently noted in toxicity studies, and these differences are taken into account when extrapolating animal toxicity to humans. Any regional permeability differences that are observed may be due to the gender- and site-related differences in the thickness of the stratum corneum and/or whole skin. For example, site- and sex-specific differences in the stratum corneum thickness in the rat, as shown in Table 2-6, may explain the results reported in Table 2-5. However, a competent stratum corneum is expected to provide better barrier capacity than a thick, disorganized stratum corneum. Thus, thickness is not the only regional variation factor in skin permeability.

Table 2-6. Rat Skin Thickness Measurement from Frozen Sections

Type of Skin	Stratum Corneum (μm)	Whole Epidermis (μm)	Whole Skin (mm)
Male			
Back	34.7 ± 2.3	61.1 ± 3.0	2.80 ± 0.08
Abdomen	13.8 ± 0.7	30.4 ± 1.5	1.66 ± 0.06
Female			
Back	18.2 ± 1.0	31.2 ± 1.5	2.04 ± 0.05
Abdomen	13.7 ± 0.6	34.8 ± 1.8	0.93 ± 0.02

Source: Bronaugh et al. (1983)

In a small test population (3 males, 3 females), 0.3% commercial lindane emulsion was applied over the entire body surface except head and elbow angle. Gas chromatography-determined blood serum levels in males were one-third those of females. Urine levels were approximately the same for both sexes (Zesch et al., 1982).

Gender-related studies were conducted with nitroglycerin (Keshary and Chien, 1984) and with estradiol (Valia and Chien, 1984a,b) using hairless mice. The results suggested that uptake, binding, and metabolism may be gender-related and affect mechanisms of percutaneous absorption.

As shown in Table 2-7, similar site-specific differences in skin thickness exist in humans as well.

Despite the important implications that stratum corneum thickness may have on body site-related variations in the rate or extent of percutaneous absorption, Elias et al. (1981) found site-specific variations in permeability to be directly proportional to the lipid content of the stratum corneum. This factor undoubtedly plays a significant role in determining the rate and extent of percutaneous absorption for highly lipophilic compounds.

Table 2-7. Regional Variation in Stratum Corneum Thickness in Humans

Skin Area	Stratum Corneum Thickness μm
Abdomen	15.0
Volar forearm	16.0
Back	10.5
Forehead	13.0
Scrotum	5.0
Back of Hand	49.0
Palm	400.0
Sole	600.0

Source: Scheuplein and Blank (1971)

Regional differences in the extent of percutaneous absorption can have a significant impact on calculations of dermally absorbed dose and on any subsequent risk assessment that uses these values. Guy and Maibach (1984) proposed a methodology for incorporating regional permeability differences into the assessment of dermally absorbed dose.

2.3.1.2. *Age of the Skin*

Infants and children represent a population at high risk for the toxic effects of environmental pollutants because of, among other reasons, their immature detoxification pathways and rapidly developing nervous systems. Infants and children are also at increased risk for dermal exposure to toxic compounds because of their greater surface-to-volume ratio. Reports of toxic effects occurring in infants after the topical application of various drugs or pharmaceutical agents are not uncommon in the literature. These toxic effects, however, are most likely the result of the increased surface-to-volume ratio in infants resulting in greater total absorption of the compound, rather than to the increased permeability of the skin of infants relative to adults. Full-term infants have been shown to have a completely functional stratum corneum with excellent barrier properties (Atherton and Rook, 1986).

To investigate possible age-related changes in dermal permeation, Wester et al. (1985) compared the in vitro percutaneous absorption of triclocarban in adult and newborn abdominal and foreskin epidermal preparations (split-thickness, frozen skin samples). Using a static diffusion cell system at 37°C, these researchers showed that the total dose of triclocarban absorbed across abdominal skin preparations excised from human adults, a newborn infant (5-day-old female donor) and an older infant (9-month-old male donor) was similar, as shown in Table 2-8.

Unlike full-term infants, pre-term infants may demonstrate an increased percutaneous absorption of some compounds, probably because of the lack of a fully developed stratum corneum. Barker et al. (1987) investigated the effect of gestational age on the permeability of an infant's skin to sodium salicylate. They showed that absorption of this compound across excised, full-thickness abdominal skin was several orders of magnitude greater in infants of 30 weeks of gestation or less than in full-term infants. The epidermis of these pre-term infant skin samples was thin, with relatively little formation of a keratinized stratum corneum.

Table 2-8. In Vitro Percutaneous Absorption of Triclocarban in Human Adult and Newborn Abdominal and Foreskin Epidermis

Type	Dose Absorbed (Percent ± SD)
Static system, 37°C	
Adult abdominal	0.23 ± 0.15
Newborn abdominal	0.26 ± 0.28
Infant abdominal	0.29 ± 0.09
Adult foreskin	0.60 ± 0.25
Newborn foreskin	2.5 ± 1.6
Static system, 23°C	
Adult abdominal	0.13 ± 0.05
Continuous flow system, 23°C	
Adult abdominal	6.0 ± 2.0
Human in vivo	0.7 ± 2.8

Source: Wester et al. (1985)

Although dermal permeability remains relatively invariant in humans as a function of age, at least one experimental animal species, the hairless mouse, undergoes a period early in life where the percutaneous absorption of some compounds is increased. Behl et al. (1984) reported that a three- to fivefold increase in permeability of hairless mouse skin occurs in animals less than 120 days of age relative to that observed in older animals.

At the other end of the age spectrum, older adults also constitute a high-risk category for the toxic effects of environmental pollutants. Although the effects of increasing age on the gastrointestinal absorption of toxic chemicals have been addressed, the effects of aging in humans on the percutaneous absorption of toxic compounds appear to have been largely ignored. However, Banks et al. (1989) recently reported that the percutaneous absorption of TCDD and 2,3,4,7,8-pentachlorodibenzofuran decreases as a function of increasing age in male F-344 rats. These findings suggest that the potential for systemic toxicity occurring in older animals after dermal exposure to these halogenated hydrocarbons is reduced. Behl et al. (1983b) also observed a slightly reduced permeability of hairless mouse skin from older animals (441 days) to phenol; however, these investigators concluded that any decline in permeability was probably the result of animal variability rather than age. Other recent age-related changes in rat and mouse skin have been reported by Monteiro-Riviere et al. (1991) and by Banks and Birnbaum (1991). A review of the world's literature on skin permeability as related to age suggests that age-related differences in skin permeability (child to adult) are generally less than species-related differences (mouse to human). Old and young skin appeared alike in barrier function (Marzulli and Maibach, 1984). Recent studies by Roskos et al. (1989) showed that two lipophilic compounds (testosterone and estradiol; log $K_{o/w}$ 3.3 and 2.5, respectively) were alike in penetrating aged (> 65 years) and young (18-40 years) skin; whereas hydrocortisone, benzoic acid, acetylsalicylic acid, and caffeine (log $K_{o/w}$, 1.6, 1.8, 1.3, and 0.01, respectively) were less facile in penetrating aged skin. It was speculated that a diminished amount of surface lipids in aged skin may provide increased resistance to penetration by the more hydrophilic compounds.

2.3.1.3. *Skin Condition*

For most compounds, the rate of percutaneous absorption is limited by diffusion through the stratum corneum. However, the epidermal barrier may not be intact in diseased or damaged skin. Persons with diseased or damaged skin may be at special risk for the toxic effects of environmental pollutants as a result of increased percutaneous absorption. Damage to the skin may occur from mechanical injury (cuts, wounds, abrasions) or other insults such as sunburn. Any skin condition that compromises the capability of the stratum corneum to serve as a permeability barrier, including psoriasis, eczema, rashes, or dermatitis, may also result in increased percutaneous absorption in affected individuals (Brown et al., 1984).

A number of studies have been conducted to quantify chemical absorption through abnormal skin in vitro and in vivo. Increased absorption of hydrocortisone (Solomon and Lowe, 1979) and propylene glycol (Komatsu and Suzuki, 1982) have been observed in vitro using damaged hairless mouse and rabbit skin, respectively. However, the in vitro model may be inadequate for studying this process. While increased blood flow may not affect percutaneous absorption through normal skin, it may indeed affect the absorption rate through skin denuded of stratum corneum. Also, it is not currently possible to prepare split-thickness epidermal sheets from skin in which the stratum corneum has been stripped off (Scott and Dugard, 1986). These limitations have largely restricted investigators in this field to the use of in vivo studies.

Increased in vivo absorption of mannitol and octyl benzoate have been observed in tape-stripped rat skin. Tape stripping removes the stratum corneum and provides a simple model for a psoriatic or eczematous state in skin. Using monkey skin affected by eczematous dermatitis, Bronaugh et al. (1986a) demonstrated a doubling of the total absorption of hydrocortisone across diseased skin versus that across normal skin sites. However, this effect is not seen with triamcinolone acetonide, whose absorption through normal skin is so rapid that there is no increase when applied to damaged skin. Earlier work by Bronaugh and Stewart (1985) also demonstrated that the greatest increases in skin penetration in damaged skin are observed for compounds that are poorly absorbed.

The barrier layer of the skin cannot only be damaged by disease processes or mechanical injury, but also by exposure to the chemical penetrant itself, especially at high concentrations. The effect of concentration on the permeability of the skin to a particular compound is reviewed in Section 2.3.2.

2.3.1.4. *Hydration*

As discussed previously, the thickness of the stratum corneum is a major determinant of the dermal permeation. The permeability is inversely proportional to the thickness of the stratum corneum. However, thickness of the stratum corneum in vivo and in vitro is positively correlated with the relative environmental humidity and degree of hydration of this layer.

Therefore, one would expect well-hydrated skin to be less permeable than relatively dry skin as a result of its increased thickness. This, however, is not generally the case. As a rule, hydration increases the permeability of skin for most compounds. Therefore, there is an increased potential for percutaneous absorption of environmental pollutants in scenarios such as bathing, swimming, or showering where the skin is well hydrated.

2.3.1.5. *Circulation to the Skin*

Prolonged skin exposure to organic solvents is known to result in vasodilation in areas that come into contact with these compounds (e.g., Engstrom et al., 1977). If the rate of chemical accumulation in the epidermis (via diffusion across the stratum corneum) is equal to or greater than the circulatory perfusion rate, then the rate-limiting step for skin permeation could become that of capillary transfer. The relationship between the rates of capillary transfer and diffusion can be described by the following equation (Scheuplein and Blank, 1971):

$$-D\,\frac{dc}{dx} = \frac{\varnothing\ (C_l - C_c)}{L} \qquad (2.1)$$

where:

D = Average membrane diffusion coefficient (cm^2/min.); and

$\frac{dc}{dx}$ = Change in chemical concentration over the change in unit distance through the layers (mg/cm^2).

$\varnothing$ = Peripheral blood flow (mL/min.);

C_t = Concentration of the diffusing compound in tissue adjacent to the capillary walls;

C_c = Concentration (ng/mL) of the diffusing compound in capillary blood;

L = Thickness (cm) of the capillaries below the stratum corneum;

The ratio of $\varnothing/L$ represents the transfer coefficient (for the epidermal-dermal junction) into capillary circulation and, in practical terms, is inversely proportional to the resistance of capillary wall permeability. If this resistance is small relative to resistance to diffusion across the stratum corneum, then the latter would be the rate-limiting step. For all situations except those involving gases and small, highly lipophilic compounds, the diffusion resistance (across the stratum corneum) is likely to be substantially greater than capillary resistance. Thus, circulatory flow should not be rate-limiting in most cases.

2.3.1.6. *Skin Temperature*

Humans who are exposed to ambient or drinking water supplies during activities such as bathing, showering, or swimming may differ markedly in skin surface temperature. Therefore, it is important to consider the potential impact that water temperature may have on the rate or extent of percutaneous absorption of the compound of interest.

Jetzer et al. (1988) recently examined temperature-related changes in K_p using hairless mouse skin in a diffusion cell apparatus. Their results for three model compounds are presented in Table 2-9.

Keeping the receptor solution at 37°C to mimic the physiological state, but exposing the stratum corneum to aqueous solutions of the compound at temperatures from 10°C to 37°C allowed these investigators to evaluate the effect of environmentally relevant exposure scenarios with this in vitro test system. As shown in Table 2-9, for these three compounds, K_p varies three- to seven-fold as a function of donor solution temperature. Durrheim et al. (1980), as well, have shown that percutaneous absorption rates can vary over the temperature range of 29°C to 37°C. At the other end of the temperature spectrum, Liron and Cohen (1984a) reported a two-fold increase in K_p in vitro going from a donor solution temperature of 37°C to 50°C. Therefore, the potential exists for percutaneous absorption to increase in vivo when skin temperatures are elevated during bathing or showering with warm water. Frequently, in the absence of skin damage, a 10-fold increase in temperature results in a doubling of skin permeability. Depending on the magnitude of activation energy for diffusion, an increase in temperature may result in a different extent of increase in skin permeability.

Table 2-9. Effect of Temperature on Permeability Coefficients for Model Compounds Permeating Hairless Mouse Skin In Vitro

Permeant	Temperature (°C) of Donor[a]	K_p [cm/hr] (± s.d.)
n-Butanol	10	0.00237 (0.00117)
	20	0.00470 (0.00025)
	30	0.00805 (0.00180)
	37	0.01432 (0.00239)
Phenol	10	0.01602 (0.00109)
	20	0.01932 (0.00270)
	30	0.02881 (0.00148)
	37	0.04375 (0.00020)
p-Nitrophenol	10	0.00289 (0.00033)
	20	0.00608 (0.00046)
	30	0.00109 (0.00010)
	37	0.01753 (0.00237)

[a] Receptor fluid temperature = 37°C.

Source: Jetzer et al. (1988)

These results suggest that the exposure/risk assessor should take environmental and skin temperature into consideration when using the K_p values to estimate dermally absorbed dose in specific exposure scenarios; however, this factor probably changes K_p values by less than an order of magnitude.

2.3.1.7. *Miscellaneous Factors*

In addition to the variables discussed in this section, there are several other factors that may affect the rate and degree of skin penetration, including the release rate of the compound from the vehicle in which it is formulated and multiple versus single-dose application. These factors are potentially important and should be considered by the exposure/risk assessor where applicable. For a more detailed examination of these topics, the reader is directed to reviews that address these topics in greater detail (e.g., Wester and Maibach, 1983).

2.3.2. Compound-Specific Factors

In addition to the skin-specific factors discussed above, the physico-chemical nature of the penetrant compound also plays a role in the rate and extent of absorption of that compound. These factors are reviewed below.

2.3.2.1. *Partition Coefficients*

The best penetrants are those that are soluble in both lipids and water; whereas, compounds that are largely soluble only in either lipids or water, but not both, are not as good penetrants. The relative solubility of a compound in an organic or water phase can be represented by a partition coefficient. Several investigators have attempted to demonstrate a correlation between percutaneous absorption and partitioning behavior. The use of this approach to predict K_p from partitioning behavior is explored in Chapter 5; however, the results reported in Table 2-10 by Roberts et al. (1977) are illustrative of these efforts. As shown in Table 2-10, K_p values tend to increase with increasing lipophilicity. This relationship also exists for compounds such as steroids (Scheuplein et al., 1969).

Table 2-10. In Vitro Permeability Coefficients and Partition Data for Various Phenol Compounds

Solute	K_p (cm/min)	K_p (cm/hr)	Log $K_{o/w}$
Resorcinol	0.000004	0.00024	0.8
4-Nitrophenol	0.000093	0.0056	1.96
3-Nitrophenol	0.000094	0.0056	2.00
Phenol	0.000137	0.0082	1.46
Methyl hydroxybenzoate	0.000152	0.0091	1.96
m-Cresol	0.000254	0.015	1.96
o-Cresol	0.000262	0.016	1.95
p-Cresol	0.000292	0.018	1.95
Naphthol	0.000465	0.028	2.84
Chlorophenol	0.000551	0.033	2.15
Ethylphenol	0.000581	0.035	2.40
3,4-Xylenol	0.000600	0.036	2.35
Bromophenol	0.000602	0.036	2.59
Chlorophenol	0.000605	0.036	2.39
Thymol	0.000880	0.053	3.34
Chlorocresol	0.000916	0.055	3.10
Chloroxylenol	0.000984	0.059	3.39
2,4,6-Trichlorophenol	0.000990	0.059	3.69
2,4-Dichlorophenol	0.001001	0.060	3.01

Source: Roberts et al. (1977)

The most commonly used measure of partitioning behavior is the octanol:water partition coefficient ($K_{o/w}$) or its logarithmic form (log $K_{o/w}$). However, discrepancies have been noted in the relationship between skin permeability and lipophilicity as expressed by the log $K_{o/w}$ for some compounds, notably certain phenols (Jetzer et al., 1986). This lack of correlation is particularly striking for the nitrophenols. However, when "oil"/water partition coefficients based on either *n*-

hexane, dichloromethane, chloroform, or silicone rubber as the water-immiscible phase are used, permeability coefficients for the various phenolic compounds follow the expected dependency on partitioning (Jetzer et al., 1986). On this basis, it appears that the log $K_{o/w}$ may not always properly reflect the lipophilicity of certain classes of chemicals, and, thus, may be an inconsistent predictor of skin permeability. Furthermore, these various partition coefficients are in themselves individual and unique measures of lipophilicity and should not be used interchangeably.

2.3.2.2. *Polarity*

The capacity of a substance to penetrate the skin is at least partially dependent on the polarity of a compound; that is, the extent to which the substance, at a molecular level, is associated with a nonsymmetrical distribution of electron density. Polar compounds are generally poorly absorbed through the skin, whereas nonpolar compounds are more readily absorbed. The extent of the polarity of a molecule can be expressed quantitatively through its dipole moment, which is a function of the magnitude of the partial charges on the molecule and the distance between the charges. The degree of polarity associated with a molecule is a function of spacing and proportion of electronegative atoms (e.g., nitrogen, oxygen, and fluorine), particularly if they are ionizable, versus the occurrence of nonelectronegative atoms (e.g., hydrogen, carbon). Thus, placing an electronegative functional group on a nonpolar compound will increase its polarity, but in many cases, the molecular size and structure will also determine a compound's polarity. The greater the polarity of a compound, the lower is the lipophilicity; lipophilicity can most readily be measured based on partition coefficients (see above).

The most polar compounds (i.e., those least able to penetrate the skin) are those that spontaneously dissociate to form ions in an aqueous environment; such compounds are referred to as electrolytes. Electrolytes can be inorganic salts, which are readily dissociated, or weak organic acids and bases, whose state and extent of ionization depend on the pH of the environment. Weak organic acids or bases in their non-ionized form are much more soluble in lipids and are absorbed more readily through the skin than when in their ionized forms. Generally, the smaller the pK_a for an acid and the larger the pK_a for a base, the more extensive will be the dissociation in aqueous environments at normal pH values, and the greater will be the electrolytic nature of the compound. Thus, the potential for absorption through the skin can be at least qualitatively determined from the ratio of ionized to unionized compound as defined by the Henderson-Hasselbach equation:

$$pH = pK_a + \log \frac{[ionized]}{[unionized]} \tag{2.2}$$

Several investigators have shown that electrolytes in dilute solution (and therefore in the ionized form) penetrate the skin poorly. It is interesting to note that small ions such as sodium, potassium, bromine, and aluminum penetrate the skin with permeability constants of about 10^{-3} cm/hour, similar to the rate reported by Scheuplein (1965) for water. Wahlberg (1968) and Skog and Wahlberg (1964) reported similar results for the chloride salts of cobalt, zinc, cadmium, and mercury; sodium chromate; and silver nitrate applied to guinea pig skin in vivo or in vitro.

However, larger nonpolar compounds that would be expected to exist as non-electrolytes in aqueous solution (e.g., urea, thiourea, glucose, and glycerol) permeate nude mouse skin in vitro with K_p values on the order of 10^{-4} cm/hour (Ackermann and Flynn, 1987).

Since the ionization state is a function of the pH of the applied solution, changes in pH can affect the penetration of an ionizable compound. For example, Wahlberg (1971) showed marked variations in the absorption of chromium from unbuffered solutions with a wide range of pH values when applied to guinea pig skin. The dramatic effect that ionization state can have on permeability was demonstrated by Huq et al. (1986) for a series of phenolic compounds as shown in Table 2-11.

As shown in Table 2-11, essentially no 2,4-dinitrophenol permeates hairless mouse skin in vitro in aqueous solution at pH levels comparable to those found in environmentally relevant dermal exposure scenarios. In contrast, at pH levels at or below the pK_a for this compound, mouse skin is fairly permeable to 2,4-dinitrophenol.

In addition, if the pH value of the applied solution results in very acidic or alkaline conditions on the skin, there is a potential to increase the rate of absorption of a compound because of destruction of the barrier layer (Zatz, 1983).

Table 2-11. Permeability of Hairless Mouse Skin to Selected Phenols as a Function of pH

Permeant	pK_a	Donor pH	K_p (cm/hr)
4-Nitrophenol	7.15	3.46	0.0012
		6.20	0.0011
		7.56	0.0007
		10.16	0.00005
2,4-Dinitrophenol	3.96	2.0	0.0151
		3.5	0.0116
		3.5	0.0105
		4.35	0.00506
		4.65	0.00326
		6.0	0.000315
		7.7	0.0[a]
2,4,6-Trichlorophenol	6.0	5.0	0.0174
		6.0	0.0087
		7.4	0.00409

[a] Significant figures not reported.

Source: Huq et al. (1986)

2.3.2.3. *Chemical Structure*

Changes in chemical structure across a series of homologous compounds have the potential to alter the permeability characteristics of these compounds. For example, Blank et al. (1967) demonstrated the effect of increasing chain length on the permeability coefficient of aqueous solutions of normal alcohols (Table 2-12). This change in K_p is most likely a result of the increase in lipophilicity.

Schaefer et al. (1987) also have shown how minor modifications in chemical structure can markedly alter the percutaneous absorption of a series of closely related androgens. For example, the addition of two hydrogen molecules to a double bond in the A ring of testosterone to yield dihydrotestosterone, results in a 30-fold decrease in the relative absorption of the latter compound over the former.

Table 2-12. Permeability of Human Skin (In Vitro) to Alcohols

Compound (Aqueous Solutions)	K_p^a (cm/hr)	Log $K_{o/w}$
Methanol	0.0005	-0.77[b]
Ethanol	0.0008	-0.31[b]
Propanol	0.0014	0.30[c]
Butanol	0.0025	0.65[b]
Pentanol	0.0060	1.56[b]
Hexanol	0.0130	2.03[b]
Heptanol	0.0320	2.41[b]
Octanol	0.0520	2.97[b]
Nonanol	0.0600	3.47[d]

[a] Blank et al. (1967)

[b] Hansch-Leo Log P Database (online database). Pomona College Medicinal Chemistry Project (data from hard copy printout).

[c] Information System for Hazardous Organics in Water (online database). Baltimore, MD: Chemical Information System.

[d] CHEMEST or AUTOCHEM estimation.

The marked changes in percutaneous absorption that may result from small structural differences point out the potential error of using values for structurally similar compounds in dermal exposure assessment, in the absence of experimentally derived values for the compound of interest.

Except for compounds of molecular weight of 400 or more, the molecular size and weight of a compound appear to have less of an effect on the rate or extent of percutaneous absorption than lipophilicity. Large macromolecules penetrate skin slowly because of a combination of molecular size and poor lipid solubility. Summarizing the work of several researchers, Grasso and Lansdown (1972) noted that macromolecules such as colloidal sulfur, albumin, dextran, and polypeptides penetrate the skin poorly if applied in an aqueous solvent. However, these macromolecules will permeate the skin more readily if applied in a solvent with high lipid solubility.

2.3.2.4. *Volatility*

As mentioned in Section 2.2.2., volatilization of a compound from the surface of the skin represents a process that may result in loss of the applied compound. Since volatilization of the compound will alter the amount on the skin surface available for absorption, estimates of percutaneous uptake should account for this loss process.

Volatilization can be prevented in experimental studies by the application of occlusive wraps or devices over the site of compound exposure. However, occlusion generally results in enhanced absorption of the test compound. The relevance of absorption data obtained in studies where occlusive wraps or devices are used must be assessed when the data are to be used in exposure/risk assessment, because they may result in overestimates of percutaneous absorption.

2.3.2.5. *Compound Concentration*

A major determinant of the amount of a compound absorbed across the skin is the concentration or the amount of the compound at the skin surface. Wester and Maibach (1976) demonstrated that the total amount of a compound absorbed increases as a function of the applied amount per unit area, as shown in Table 2-13. Taylor (1961) estimated that at least 1 mg/cm^2 liquid must be applied to fill the holes in surface of skin. Above this amount an applied liquid forms a pool on the skin surface.

Furthermore, when Fick's first law of diffusion is applicable, skin penetration at steady state is proportional to the concentration (driving force) of the penetrant (Tregear, 1966). Fick's first law does not apply when the penetrant damages the skin.

Liron and Cohen (1984a) reported that the penetration of propionic acid from *n*-hexane solution through porcine skin in vitro was relatively high at higher concentrations. The authors postulate that this effect may be the result of a breakdown of the skin barrier by exposure to the acid used in the study.

Table 2-13. Percutaneous Absorption of Topical Doses of Several Compounds in the Rhesus Monkey

Acid[a] Time (hr)	Testosterone ($\mu g/cm^2$)					Hydrocortisone ($\mu g/cm^2$)	Benzoic ($\mu g/cm^2$)	
	40	250	400	1600	4000	40	40	2000
0-24	2.5[b]	0.5	0.5	0.5	0.1	0.9	29.9	13.5
24-48	1.7	1.2	0.8	1.2	0.5	0.7	3.0	2.8
48-72	1.1	0.6	0.4	0.5	0.3	0.3	0.4	0.7
72-96	0.8	0.4	0.3	0.4	0.3	0.1	0.2	0.3
96-120	10.6	0.2	0.2	0.3	0.2	0.1	0.1	0.2
Total %	6.7	2.9	2.2	2.9	1.4	2.1	33.6	17.4
SD	4.2	1.4	1.0	1.7	0.8	0.6	5.1	1.2
Total μg	2.7	7.2	8.8	46.4	56.0	0.84	134.4	348.0
Number of animals	6	3	3	3	3	3	3	3

[a] Values for benzoic acid are not corrected for incomplete urinary excretion. All other values (that is, for the other chemicals) are corrected.

[b] All data are presented as the percentage of the applied dose that was absorbed.

Source: Wester and Maibach (1976)

The skin barrier can also be damaged by the delipidizing effect of organic solvents. Numerous investigators (Scheuplein and Blank, 1973; Roberts et al., 1977; Baranowska-Dutkiewicz, 1982; Behl et al., 1983b; Huq et al., 1986) demonstrated increased flux rates for various compounds which dissolved in organic solvents across both human and animal skin relative to the permeability of more diluted aqueous solutions of the same compounds. Each of these researchers attributed this increased permeability to the delipidization and subsequent damage of the stratum corneum.

2.4. SUMMARY AND CONCLUSIONS

In summary, this chapter has reviewed the structure of human skin and identified physico-chemical properties that govern the entry of topically applied chemicals into the body. The key conclusions and research recommendations are summarized below.

Animal studies and in vitro evaluations provide useful models for exploratory experiments on skin, but the use of human skin in vivo is often needed as follow-up to confirm impressions gained from models.

2.4.1. Structure

Thin layers of semicrystalline lipid surround the compact cellular layers filled with keratin that comprise the stratum corneum, the outermost skin structure encountered by topically applied chemicals. Transport of substances through this two-phase, protein-lipid barrier tissue is thought to involve a transcellular (aqueous) and an intercellular (lipid) pathway.

2.4.2. Fate

The protein-lipid multilayered stratum corneum provides the first and main barrier to skin penetration. The underlying viable epidermis provides the second barrier, and a small thickness of papillary dermis that separates the viable epidermis from the capillaries encased in the dermal papillae provides a third barrier.

When a substance is applied to skin, some of it evaporates, the rest may bind or react with the skin's phases, and/or metabolize in the viable epidermis prior to being absorbed into capillary vessels of the papillary (outer) dermis.

When Fick's first law of diffusion is applicable (penetrant causes no damage to skin), the concentration gradient of the penetrant across skin provides the driving force for penetration and the rate of penetration at steady state is proportional to concentration.

The stratum corneum provides its greatest barrier function against hydrophilic compounds; whereas, the viable epidermis/papillary dermis composite is most resistant to highly lipophilic compounds. This suggests the existence of aqueous and lipid barriers from skin surface to blood stream. Additional research is needed to amplify the role of the viable epidermis/papillary dermis composite during the percutaneous transport of lipophilic compounds.

One working hypothesis for percutaneous absorption considers that this is a process that is largely governed by the interaction of physico-chemical factors of both the penetrant and the skin. Solubility of the penetrant chemical in water and in lipids is the first factor. Traversal of aqueous or lipid pathways is the second. Compounds naturally diffuse across the path of least resistance to them so that those that are only water-soluble traverse the skin largely via the aqueous pathway; whereas, those that are fat-soluble employ the lipid pathway. Chemicals with both lipid and aqueous solubility traverse the skin via both pathways.

The aqueous pathway is a most resistant pathway and neat water-soluble compounds have a human skin permeability constant that is unlikely to exceed 0.001 cm/hour. The lipid pathway is more facile than the aqueous pathway, and neat fat-soluble compounds have a higher rate of penetration than neat polar compounds.

The most facile skin penetrants are those that exhibit fat- and water-solubilities and low levels of crystallinity such as DMSO, benzoic acid (MP 122°C), and caffeine (MP 238°C).

It is instructive that benzoic acid, an organic acid with fat- and water-solubility is a good skin penetrant; whereas, nicotinic acid (MP 237°C), a related organic acid with a nitrogen added to a similar ring structure is water-soluble, insoluble in lipids, higher melting, and a poor skin penetrant.

2.4.3. Factors

Many factors can affect skin penetration and deserve reflection as to their importance. Some of these factors can significantly influence the outcome of a dermal exposure and risk assessment while others have a relatively small influence. Accordingly, the factors covered in this chapter have been divided into those of first-order and second-order importance. Considering the large uncertainties involved in conducting dermal exposure and risk assessment, only those factors of first-order importance need to be considered in developing quantitative exposure and risk assessments. The secondary factors could be used to fine tune an assessment or simply considered qualitatively. It goes without saying, that the skin should be intact. In addition, the solvent system penetrant concentration, its volatility, binding capacity to keratin, partition coefficient, and metabolic capacity are also of first-order importance. Other factors that indeed may affect skin penetration, such as skin site, skin thickness, skin hydration, skin temperature, skin circulation, and skin age are likely to be of secondary importance and need not enter into exposure and risk calculations unless specific information is available that warrants it. Specific conclusions relating to these factors are discussed below.

The capacity of skin to metabolize topically applied compounds varies with the chemical and the species involved. Steroids and polycyclic aromatic compounds are among those chemicals that can be metabolized by skin. In some cases, skin metabolism affects skin penetration after it has changed the solubility characteristics of the penetrant compounds. Limited studies suggest that human skin may not be as active in this regard as animal skin, but this needs further substantiation. As it is possible that skin microflora may metabolize topically applied compounds, this potential bears investigation.

Finally, it is important to note that organic lipids such as benzene penetrate skin differently when applied neat than when applied in aqueous solution or, for that matter, as solutions in any solvent. In the first instance, the permeation of the neat compound operates at maximal thermodynamic activity. Kinetically, the neat solvent's high self-concentration allows it to keep the skin's surface saturated as absorption proceeds. Additionally, its imbibition causes the compound to solubilize itself, further steepening the concentration gradient.

High fluxes are invariably achieved although permeability coefficients, which are concentration normalized parameters, may appear small. In the instance of an aqueous solution, the concentration of the benzene is necessarily low due to its low intrinsic solubility in water, although its thermodynamic activity may still be high and approach that of neat liquid if the benzene is at or near a saturated state. Nevertheless, the presence of water affects the skin differently, possibly expanding the polar pathway. Regardless, the low concentration of benzene with a high activity necessarily means the permeability coefficient will be large. This results in a higher permeability coefficient for water-dissolved benzene than for neat benzene, i.e., 0.2 vs. 0.002 cm/hour.

As the components of skin are thought to bear a relation to penetrant capacity, the octanol-water ($K_{o/w}$) partition coefficient is commonly employed for this purposes. There are limitations in the usefulness and accuracy of this predictive measure, however, and further research is needed. (The $K_{o/w}$ for neat lipid compounds does not correspond to the value for water-dissolved lipids.)

Exploratory skin penetration studies involving different regions of the body suggest that skin thickness may be less important than lipid-protein makeup in determining the absorption of compounds through different body sites. In vivo data with water-insoluble compounds (malathion and hydrocortisone) showed that the thick palmar stratum corneum was no more resistant to penetration by these compounds than the anterior forearm. On the other hand, in vitro data with more water-soluble compounds showed that thick plantar skin was more protective than anterior forearm skin.

Further work is needed to identify anatomical and physico-chemical differences in palmar or plantar and anterior forearm skin that contribute to their barrier capacities.

Covering the skin with an occlusive wrap restricts evaporation and promotes hydration of the skin. Both factors may contribute to increased absorption of topically applied substances.

Hydration of skin, temperature, and age are factors that should be considered. Hydration by occlusion may increase skin absorption of some compounds about twofold. A ten degree rise in skin temperature may also increase skin absorption twofold depending on the physico-chemical properties of the penetrant. Age may have importance only if premature infants with incompletely developed skin barriers are involved. However, recent work in rats, mice, and human suggest that additional work is needed to investigate age effects using a variety of compound types.

Skin strata thicknesses are expected to have some bearing on skin penetration since diffusion through any membrane is proportional to its thickness. On the other hand, when it comes to stratum corneum thickness differences, changes in the quality of the membrane may override the effects of thickness. A well-developed, thin stratum corneum may offer greater penetration resistance than a poorly developed, thick stratum corneum.

Generally speaking, large molecules are less competent in traversing the skin than small molecules, if other physico-chemical properties are alike. Some high molecular weight macromolecules (such as albumin, dextran, and colloidal sulfur) are said to penetrate skin more readily from solvents of high lipid solvency. Additional research is needed in this area to understand how macromolecules are, in fact, absorbed through skin.

Out of aqueous solution, ionic forms do not penetrate skin as readily as their unionized forms. Clearly the unionized form is more lipid-soluble and this seems to be the governing factor. However, organic salts may penetrate from nonaqueous media in the form of ion pairs, and have surprisingly high fluxes. For a molecule that is dissociable in water, the pK_a and pH of the solution determine the proportion of ionized and non-ionized forms. This affects partition coefficient and permeability.

3. TECHNIQUES FOR MEASURING DERMAL ABSORPTION

The permeability coefficient (K_p) and percent absorbed values presented in this document have been generated from both in vivo and in vitro studies that utilized a wide range of experimental techniques. Ideally, the absorption rate values used in a percutaneous exposure assessment should be obtained under conditions that mimic environmentally relevant exposure scenarios. However, few studies of this nature have been conducted. Studies of human subjects are very costly, and the conditions of the experiment more difficult to control. Also, ethical constraints may rule out the testing of toxic compounds in humans. In the absence of human in vivo percutaneous absorption values, exposure/risk assessors are required to use available data from in vivo animal and in vitro animal or human studies. The challenge, therefore, is to extrapolate the results obtained in animal studies to those expected in humans, and to evaluate the capability of in vitro percutaneous absorption rate values to predict the percutaneous absorption of toxic compounds in vivo. This chapter will examine these issues and provide a set of general guidelines for evaluating absorption data for use in a cutaneous exposure assessment.

Because of the wide variation in the experimental techniques used to obtain percutaneous absorption rate data, exposure/risk assessors are urged to examine the relevance of the available data for their particular exposure scenario when estimating percutaneously absorbed dose. For example, since rat skin is generally three to five times more permeable than human skin, the use of K_p or percent absorbed data from rat studies may result in a conservative (i.e., higher) estimate of percutaneously absorbed dose in humans. Conversely, variation in the thickness of the stratum corneum at different body sites may cause the exposure/risk assessor to underpredict the K_p or percent absorbed for whole-body exposure if data from whole-hand immersion studies are used. Therefore, it is important to be aware of factors that affect the rate or extent of absorption when conducting a cutaneous exposure assessment. Many factors, such as body site variation, skin metabolism, and binding in the skin, have been addressed in Chapter 3. Other factors that may limit the use of K_p or percent absorbed values in cutaneous exposure assessment are inherent in the experimental technique used to obtain the values or the design of the study. To assist exposure/risk assessors in their selection of the most valid K_p values, the studies considered in this document are categorized by the experimental technique listed in Table 3-1. This chapter will review these techniques and examine various factors that may affect how data generated using these methods can

Table 3-1. Experimental Techniques Used to Obtain K_p or Percent Absorbed Values

Technique[a]	Reference[b]
IN VIVO	
Quantification of Radioactivity, Parent Compound or Metabolites in Excreta	Baranowska-Dutkiewicz, 1982 Bronaugh and Stewart, 1986 Dutkiewicz and Tyras, 1967, 1968 Engstrom et al., 1977 Guest et al., 1984
Quantification of Radioactivity or Parent Compound in Blood, Plasma or Tissues	Engstrom et al., 1977 Guest et al., 1984 Johanson et al., 1988 Skog and Wahlberg, 1964
Quantification of the Disappearance of the Compound from the Surface of the Skin or from the Donor Solution	Baranowska-Dutkiewicz, 1981, 1982 Dutkiewicz and Tyras, 1967 Fredericksson, 1961a,b Knaak et al., 1984a,b Lopp et al., 1986 Skog and Wahlberg, 1964 Wahlberg, 1971
Measurement of a Biological Response	Fredericksson, 1961a
IN VITRO	
Diffusion Cell/Quantification of Radioactivity in Receptor Solution	Ackerman and Flynn, 1987 Behl et al., 1983a,b, 1984 Bond and Barry, 1988 Bronaugh and Stewart, 1986 Bronaugh et al., 1986a,b DelTerzo et al., 1986 Durrheim et al., 1980 Fredericksson, 1961b Garcia et al., 1980 Guest et al., 1984 Huq et al., 1986 Jetzer et al., 1986, 1988 Lopp et al., 1986 Shackelford and Yielding, 1987 Scheuplein and Blank, 1973 Scott et al., 1987

(continued on the following page)

Table 3-1. (continued)

Technique[a]	Reference[b]
Diffusion Cell/Quantification of Parent Compound in Receptor Solution	Blank and McAuliffe, 1985 Blank et al., 1967 Dugard et al., 1984 Huq et al., 1986 Jetzer et al., 1986, 1988 Roberts et al., 1977 Scheuplein and Blank, 1973 Scott et al., 1987 Southwell et al., 1984 Tsuruta, 1977, 1982

[a] Techniques for studies that provided K_p values for chemical vapors are described in Chapter 7.
[b] Citations as they appear in the reference list.

be used in a cutaneous exposure assessment. These factors are summarized in Table 3-12 at the end of this Chapter. This chapter focuses on techniques to obtain K_p or percent absorbed values for compounds applied to the skin in neat form or in various liquid vehicles. Chapters 6 and 7 have been included to examine the methods used to quantify the percutaneous absorption of soil contaminants and vapors, respectively.

3.1. IN VIVO STUDIES

Quantitative percutaneous absorption rate values can be obtained in living animals and humans using a variety of techniques. The application of the compound of interest to the skin in vivo may be more physiologically relevant than the use of in vitro methods. However, in vivo techniques allow only indirect measurement of the absorption of the compound across the skin. Also, the results of in vivo studies are often reported as the percent of the applied dose that is absorbed, thereby limiting their use for cutaneous exposure assessment, if a K_p is required.

Various authors (Wester and Maibach, 1986, 1989a; Scott and Dugard, 1989) have reviewed the advantages and limitations of many of the techniques available to obtain in vivo percutaneous absorption rate values. These advantages and limitations are summarized below.

3.1.1. Quantification of Radioactivity, Parent Compound, or Metabolite Levels in Excreta (Indirect Method)

Percutaneous absorption is commonly determined by measuring the appearance of radioactivity in the excreta following the topical application of a labeled compound. Following application of the radiolabeled compound, the total amount of radioactivity excreted in urine or urine plus feces is determined. The total radioactivity in the excreta is a mixture of the parent compound and any labeled metabolites that may have resulted from metabolism of the parent in the skin and the body.

Any radioactive label retained in the body, or excreted by another route, will not be detected in the urine or feces. Therefore, Feldmann and Maibach (1969, 1970, 1974) used the following expression to correct for any nonassayed radioactivity:

$$\textit{Percent Absorbed} = \frac{\textit{Total radioactivity following topical administration}}{\textit{Total radioactivity following parenteral administration}} \times 100 \qquad (3.1)$$

The percutaneous absorption of a large number of compounds has been quantified using this technique. However, since absorption is expressed as percent of the applied dose, none of the K_p values considered in this document result from studies that employed this approach. As the percent absorbed may vary with different amounts applied, it is desirable that the actual dosing regimen is reported.

An alternative to measuring the amount of radioactive label in the excreta involves measuring levels of a urinary metabolite over time. For example, Baranowska-Dutkiewicz (1982) estimated the percutaneous absorption of aniline based on the amount of *p*-aminophenol excreted in the urine over a 24-hour period. Similarly, Dutkiewicz and Tyras (1967, 1968) estimated the percutaneous uptake of ethylbenzene and styrene from the appearance of mandelic acid in the urine of exposed individuals. Use of this technique to quantify percutaneous absorption requires that the urinary metabolites of a parent compound be known, and the relationship between administered dose of the parent compound and amount of the metabolite in the urine be characterized.

3.1.2. Quantitation of Radioactivity, Parent Compound, or Metabolite Levels in Excreta, Air, and Tissues (Direct Method)

In contrast to the indirect method described above, percutaneous absorption has been directly determined by actually measuring absorbed material excreted in the air or remaining in the body tissues at the end of an experiment (in addition to the material excreted in the urine and feces). Summing all the absorbed material gives a direct measurement of absorption (Shah and Guthrie, 1983; Yang et al., 1986a). Similar results were obtained in a comparison of the direct and indirect methods (Shah and Guthrie, 1983). The direct method obviates the need for extrapolation with a correction factor. However, tissue levels can only be obtained at the time of sacrifice of the animal.

3.1.3. Quantification of Parent Compound or Metabolite in Blood, Plasma, or Tissues

In some cases, unlabeled parent compound can be measured in blood, plasma, or tissues after topical administration (Chien et al., 1989; Corbo et al., 1990). However, because of the difficulty in detecting and quantifying low levels of many compounds in the plasma, this approach has been used for only a few compounds.

Wester and Maibach (1983) measured actual levels of nitroglycerin (NTG) in the plasma after topical administration in addition to following the radiolabel. These investigators estimated the mean percutaneous absorption of this drug using three measurements: (1) area under the curve (AUC) of the plasma NTG concentration-time profile; (2) AUC of the total radioactivity in the plasma; and (3) urinary total radioactivity. Their results are presented in Table 3-2.

Wester and Maibach (1983) speculated that the difference between the percutaneous absorption based on the AUC of the parent compound in the plasma and percutaneous absorption based on the measurement of total radioactivity in either plasma or urine is due to the first-pass metabolism of this compound occurring in the liver.

Table 3-2. Comparison of in vivo Methods for Determining Mean Bioavailability

Method	Percutaneous Absorption (%)
Plasma nitroglycerin AUC	56.6 ± 2.5
Plasma total radioactivity AUC	77.2 ± 6.7
Urinary total radioactivity	72.7 ± 5.8

Source: Wester and Maibach (1983)

Radioactivity can be measured in the tissues, as well as in blood or plasma, after topical administration of a compound. This approach can be used not only to characterize the tissue distribution of the radiolabel after cutaneous exposure (e.g., Skowronski et al., 1989), but also to quantify the rate or extent of absorption. For example, Poiger and Schlatter (1980) determined the extent of percutaneous absorption of TCDD in a soil matrix applied to the backs of hairless mice by monitoring the appearance of radiolabel in the liver. Shu et al. (1988) conducted a similar study of percutaneous absorption of TCDD applied in soil. However, estimation of the percent of TCDD absorbed in these studies requires knowledge of the distribution of compound in the body and the percent of the body burden of the compound that resides in the liver.

3.1.4. Quantification of the Disappearance of the Compound from the Surface of the Skin or from the Donor Solution

An older technique used to measure in vivo percutaneous absorption involves determining the loss of material from the surface as it penetrates the skin. It is assumed that the difference between applied dose and residual dose is the amount of penetrant absorbed. The difficulties inherent in skin recovery, volatility of penetrant, and errors associated with using the difference between the amount of the compound applied and the amount remaining make this an inaccurate method to obtain quantitative percutaneous absorption rate information. As shown by Frederickson (1962), this approach can be especially problematic for compounds that permeate the skin slowly.

Percutaneous absorption rate constants for several important environmental pollutants (e.g., ethylbenzene, toluene, styrene, xylene) were obtained by measurement of the disappearance of the compound from the donor vehicle (Dutkiewicz and Tyras, 1967). Any difference in the amount of the compound in the donor solution before and after immersion of the whole hand in the liquid for a prescribed period is assumed to result from uptake across the skin. Evaporation of the compound is prevented by placing a beaker containing the donor solution in a polyethylene bag and securing the open end of the bag around the subject's forearm.

The studies conducted by Dutkiewicz and Tyras (1967, 1968) using this technique are of special interest because they have generated K_p values for important environmental pollutants using human subjects and aqueous solutions of the compounds. Furthermore, the values generated by this technique have been used by other investigators to determine the relative contribution of percutaneous absorption to total body burden (Brown et al., 1984; Shehata, 1985; Brown and Hattis, 1989) or to validate theoretical skin permeability models (Brown et al., 1990). Several researchers, however, have identified problems inherent in this approach. Sato and Nakajima (1978) suggested that the rate of absorption measured by Dutkiewicz and Tyras (1967, 1968) may be a combination of the rate at which the compound is absorbed by the systemic circulation and rate at which the compound is taken up by the stratum corneum. Maibach (1989) expressed similar concerns over the use of this technique to provide valid K_p values.

3.1.5. Measurement of a Biological Response

Biological or pharmacological responses have been used to estimate percutaneous absorption for a limited number of compounds. Responses such as vasodilation or vasoconstriction have been monitored as indices of compound absorption. For example, laser Doppler velocimetry has been used as a noninvasive technique to monitor the vasodilatory effects of topically applied nicotinate compounds (Guy et al., 1985; Kohli et al., 1987).

One study considered in this document uses a biological response to obtain absorption rate values. Frederickson (1961a) determined the percutaneous flux of paraoxon in cats by monitoring the inhibition of plasma cholinesterase in these animals after topical administration of the compound.

Biological responses following percutaneous absorption have recently been used to correlate with plasma levels and/or absorbed doses as follows: myocardial contractility of propranolol (Corbo et al., 1989), suppression of progesterone by levonorgestrel (Chien et al., 1989), and reduction of blood glucose by insulin (Siddiqui et al., 1987).

Biological response measurements are useful, noninvasive means for determining in vivo percutaneous absorption rates when validated. However, the responses measured by these techniques cannot be used to establish the rate of absorption, unless the dose-response relationship of the compound to produce the effect is known or has been established. Therefore, given its current state of development, this approach generally provides only a semi-quantitative index of percutaneous absorption.

3.1.6. Stripping Method

In a series of papers, Rougier et al. (1983, 1985, 1987, 1989) measured percutaneous absorption in vivo and examined the relationship between absorption and the concentration of the compound present in the stratum corneum reservoir after a relatively short exposure period. For example, Rougier et al. (1987) tested the relationship between percutaneous penetration and the amount present in the stratum corneum in vivo in humans using four organic compounds (benzoic acid sodium salt, benzoic acid, caffeine, and acetyl salicyclic acid). The first applications of radiolabeled test compound onto the skin allowed the total absorption to be determined by measuring the amounts of the chemicals excreted in the urine during the first 24 hours. The second applications 48 hours after the first, on the contralateral site of the body enabled an assessment of the total amount of the chemical present in the stratum corneum at the end of 30 minutes by tape-stripping (15 strippings with adhesive tape). Rougier et al. (1987) determined that the amount of the four compounds penetrating human skin in vivo after four days correlated well ($r = 0.97$) with the amount of compound localized in the stratum corneum 30 minutes after application.

Despite the potential usefulness of this approach, it is a relatively recent development and none of the permeability values considered in this document were obtained using this method. Although, initial findings (Rougier et al., 1983, 1985, 1987; Dupuis et al., 1986) suggest that this may prove to be a valid approach, it appears that the stripping method has been evaluated with only a few compounds which are not important environmental pollutants. Recently Tojo and Lee (1989) used the stripping method to predict the steady-state rate of skin penetration in vivo.

3.2. IN VITRO TECHNIQUES

As indicated in Table 3-1, in vitro studies provided many of the K_p values considered in this report. This may be because values in in vivo percutaneous absorption studies are more often reported as percent of the initial dose that is absorbed. In contrast, until recently results of in vitro percutaneous absorption studies were reported as K_p or percent absorbed. Because of the reliance on in vitro studies to provide K_p values, the various in vitro experimental techniques and factors that affect in vitro percutaneous absorption will be examined in this section.

Bronaugh and Maibach (1983) reported advantages of using in vitro methods for obtaining percutaneous absorption rates. For example, these techniques permit:

- Investigation of percutaneous absorption separate from other pharmacokinetic factors that affect cutaneous uptake;
- Larger numbers of assays;
- Sampling directly under the skin; and
- Measurements of the permeability of highly toxic compounds using human tissues.

Furthermore, in vitro techniques are rapid, inexpensive, and easy to perform. However, despite these methodological advantages, the conditions present in in vitro studies can be quite different from those present in the in vivo state. Because of these differences, it is important to determine the validity of using in vitro data in a percutaneous exposure assessment. To do this, the exposure/risk assessor should be aware of the advantages and limitations of each of the commonly used in vitro techniques. It will then be possible to determine which in vitro technique best represent the in vivo physiological state of the skin in order to identify the most appropriate approach to assessment of percutaneously absorbed dose.

3.2.1. Diffusion Cells

In vitro percutaneous absorption rates are most often measured using diffusion cells (e.g., glass, teflon, stainless steel). The various types of diffusion cells have recently been reviewed (Franz, 1990). Studies conducted in the 1960s and 1970s commonly employed a two-cell (side-by-side) diffusion chamber. This technique involves mounting a piece of excised skin in the chamber, putting the radiolabeled penetrant compound in one cell and a receptor fluid, usually water or saline, in an adjacent cell. Tregear (1966) commented that the validity of using excised skin in an in vitro diffusion study depends on the following three assumptions:

- Skin surface conditions in vitro are similar to those in vivo;
- The dermis does not affect penetration; and
- No living process affects permeability.

A limitation in the use of the two-chambered diffusion cell, such as the Franz cell, is that skin surface conditions may be different from those experienced by the living organism (Franz, 1975). When occluded in the diffusion cell, the skin becomes hydrated, thereby altering the permeability characteristics of the skin (Gummer and Maibach, 1991). An alternative technique that minimizes this problem uses a one-chambered unoccluded diffusion cell (Franz, 1975). The unoccluded one-chambered cell may more closely parallel in vivo skin conditions when the stratum corneum is exposed to the atmosphere (but not during swimming). Furthermore, this arrangement allows for the evaporation of volatile compounds. However, in the one-chambered cell, unless there is an excess of material applied, one measures percent absorption rather than determines a steady-state penetration rate with attendant K_p. A flow-through cell can automate sample collection, improve partitioning of water-insoluble compounds into the receptor fluid, and replenish skin nutrients to maintain the viability of skin for metabolism studies (Bronaugh and Stewart, 1985). Determination of a permeability constant from water, however, requires that the skin be covered with an aqueous solution. Therefore, either type of cell can be used equally well.

Factors such as skin surface condition (especially those that affect volatilization of the test compound), thickness of the barrier layer, and skin viability may affect the degree of percutaneous absorption in vivo and in vitro. Therefore, these factors should be considered. A variable that may affect the predictive capacity of this in vitro technique that is unique to the diffusion cell is the solubility of the penetrant molecule in the receptor fluid. This factor can also be controlled in a diffusion cell. The degree to which these factors affect the rate of in vitro percutaneous absorption in the diffusion cell apparatus, and the advantages and limitations of this technique, are examined below.

Volatility of the Test Compound

As discussed in Chapter 2, evaporation can account for a significant percentage of the total dose of a compound applied to the skin. For example, it has been shown (Reifenrath and Robinson, 1982; Hawkins and Reifenrath, 1984) that evaporation accounts for as much as 26% of the total dose of lindane applied to pig skin in a covered diffusion cell at 24°C. Therefore, volatility is a factor that should be considered.

Receptor Fluid Compatibility

While the use of saline solution in the receptor chamber of a diffusion cell may be appropriate for measurements that determine the percutaneous flux of hydrophilic compounds, it may not be appropriate for water-insoluble lipophilic compounds. In a living organism, a lipophilic compound is readily taken up by blood (a relatively lipophilic medium of large capacity) once it enters the cutaneous capillaries. In a static diffusion cell, the receptor fluid serves the same role as blood does in vivo. However, unlike in the in vivo state, the receptor compartment volume in a diffusion cell is of a finite size. If the receptor compartment volume is relatively small, and if the compound is not metabolized in the skin, the concentration gradient across the cutaneous membrane will decrease until equilibrium is approached (Riley and Kemppainen, 1985). This limitation can be improved by using a flowing receptor medium and by changing the receptor fluid to one that can serve as a better solvent for the penetrating molecule. Addition of surfactants to the receptor fluid may alter the permeability characteristics of the skin (Riley and Kemppainen, 1985).

Wester and colleagues (1985) reported that markedly different values for the percutaneous absorption of triclocarban in human abdominal skin were obtained in static and continuous flow diffusion cells (Table 3-3). The relative insolubility of this compound in the aqueous receptor phase may be responsible for the discrepancy between the results obtained by the two systems. In the continuous flow system, the extent of triclocarban absorption was similar to that measured for the in vivo penetration of this compound in humans (7.0% ± 2.8%). Because of the greatly increased saline volume, the solubility of triclocarban in the receptor fluid did not limit absorption (Wester et al., 1985; Wester and Maibach, 1986).

Table 3-3. In Vitro Percutaneous Absorption of Triclocarban in Human Adult Abdominal Epidermis

Type of System	Dose Absorbed (% ± SD)		
Static, 37°C	0.23	±	0.15
Static, 23°C	0.13	±	0.05
Continuous flow through, 23°C	6.0	±	2.0

Source: Wester et al. (1985)

Some percutaneous penetration studies have been conducted using lipophilic receptor fluids such as human and animal serum, aqueous co-solvent systems, and various surfactant solutions. Bronaugh and Stewart (1984) proposed the use of the nonionic surfactant PEG 20 oleyl ether in the receptor fluid in combination with split-thickness skin (most of dermis removed with dermatome). Only when split-thickness skin was utilized was absorption of lipophilic compounds enhanced. Increased skin penetration was obtained as compared to values obtained using serum, albumin, or alcoholic solutions, and no damage to the barrier properties of skin was detectable. However, the viability of skin is not maintained under these conditions and so metabolism cannot be studied. If viability is maintained with physiological buffer, partitioning of lipophilic compounds into the receptor will not be complete. Skin content of the compound at the end of the experiment will need to be included with receptor fluid values to determine the total absorbed test compound. The difference in the relative absorption of benzo[a]pyrene (BaP) and DDT, two relatively hydrophobic compounds, across rat skin in a diffusion cell using either saline or a nonionic surfactant solution as the receptor fluid is shown in Table 3-4.

Table 3-4. Effect of Receptor Fluid Composition on the Relative Absorption of Hydrophobic Compounds

Compound	Receptor Fluid	Absorbed Percent of Applied Dose
BaP	Normal Saline	3.7 ± 0.1
	6% PEG-20 oleyl ether in water	56.0 ± 0.9
DDT[b]	Normal Saline	1.8 ± 0.1
	0.5% PEG-20 oleyl ether in water	60.6 ± 2.9

[a] Applied in an acetone vehicle (15 μL/cm^2) to haired rat skin (300 μm).
[b] Applied in an acetone vehicle (15 μL/cm^2) to fuzzy rat skin (200 μm).

Source: Modified from Bronaugh and Stewart (1986)

As shown in Table 3-4, BaP and DDT were poorly absorbed into the saline receptor fluid; however, the presence of the nonionic surfactant in the receptor chamber markedly increased the extent to which these compounds were absorbed. By comparison, Bronaugh and Stewart (1986) determined that the in vivo percutaneous absorption of BaP and DDT was 48.3% ± 2.1% (haired rat) and 69.5% ± 1.7% (fuzzy rat), respectively.

Therefore, the exposure/risk assessor should be aware that the use of in vitro percutaneous absorption data obtained in studies in which saline was used as the receptor fluid may result in underestimates of the in vivo percutaneous absorption of lipophilic compounds. The surfactant solution is appropriate only if it does not alter permeability characteristics of the skin. The rate-limiting step for diffusion through the stratum corneum of chemicals with limited water solubility may be the transfer to the receptor fluid, especially in a static receptor system. K_p is then dependent on the stratum corneum/receptor fluid partition coefficient.

Full- vs. Split-Thickness Skin

The second of Tregear's (1966) assumptions regarding the validity of using excised skin in a diffusion cell study is that the dermis does not affect penetration. Under in vivo conditions, the greatest percentage of a compound applied to the skin will be taken up by capillaries found in the dermis at a depth of approximately 200 μm. Therefore, topically applied compounds do not have to penetrate the dermis to be absorbed. However, when full-thickness skin is used in an in vitro diffusion cell study, the compound must penetrate the stratum corneum, epidermis, and dermis before reaching the receptor fluid. Furthermore, the cutaneous microcirculation is destroyed in the preparation of skin for use in a diffusion cell.

Since skin absorption is a passive process, the rate of absorption will be inversely proportional to the thickness of the barrier layer (as shown in Equation [4.4], Chapter 4). Therefore, to ensure that in vitro percutaneous absorption rates are comparable with those measured in vivo, the excised skin prepared for a diffusion cell should be of the same thickness as the effective in vivo penetration barrier. The cutaneous layer present in the full-thickness skin samples commonly used in in vitro studies may present an artificial barrier to percutaneous absorption, especially for lipophilic compounds. Unlike the stratum corneum, cutaneous tissue is primarily an aqueous medium. Therefore, this aqueous phase represents a potential barrier to the absorption of lipophilic compounds.

A number of researchers have investigated how using full- or split-thickness skin in vitro would affect the relationship between in vitro and in vivo percutaneous absorption of hydrophilic and lipophilic compounds. Hawkins and Reifenrath (1986) examined the penetration of compounds with octanol/water partition coefficients spanning several orders of magnitude using either full- or split-thickness pig skin in vitro and compared these values to those obtained in vivo, as shown in Table 3-5. Total radioactivity was measured to determine the percent of applied radioactive dose which penetrated pig skin in vitro and in vivo.

Table 3-5. Percutaneous Absorption of Radiolabeled Compounds on Pig Skin In Vitro and In Vivo

		Percent of Applied Radioactive Dose[a]		Split Thickness	
Compound	Log $K_{o/w}$	In Vivo[b]	Whole Skin[c]	Raw[c]	Adjusted[d]
Caffeine	0.01	23 ± 9	20 ± 2	18 ± 3	21 ± 4
Benzoic acid	1.95	28 ± 6	20 ± 13	17 ± 6	21 ± 7
N,N-Diethyl-m-toluamide	2.29	9 ± 4	14 ± 4	19 ± 13	21 ± 13
Fluocinolone acetonide	2.48	6 ± 1	2 ± 1	1.1 ± 0.9	2 ± 2
Malathion	2.98	4.4 ± 0.3	16 ± 11	21 ± 6	24 ± 7
Parathion	2.98	19 ± 2	1 ± 1	12 ± 5	21 ± 5
Testosterone	3.31	6 ± 0.3	3 ± 2	9 ± 4	13 ± 5
Lindane	3.66	8 ± 1	1 ± 1	6 ± 2	9 ± 4
Progesterone	3.78	10 ± 1	1 ± 1	5 ± 2	9 ± 4

[a] The applied dose of all compounds was 4 $\mu g/cm^2$.

[b] Duration of cutaneous exposure was 48 hours, followed by 5 days of monitoring excreta for radioactivity prior to animal sacrifice and tissue analyses.

[c] Duration of cutaneous exposure was 50 hours, followed by analysis of radioactivity in the receptor fluid.

[d] Sum of the radioactivity from the dermis and the receptor fluid.

Source: Hawkins and Reifenrath (1986)

From the results reported in Table 3-5, it appears that the dermis can provide a significant barrier for highly lipophilic compounds such as lindane and testosterone. With more hydrophilic compounds, the degree of percutaneous penetration in vitro more closely approximates percutaneous permeation values obtained in vivo. Also, as might be expected, removal of the epidermal layer of pig skin in vitro enhances the percutaneous absorption of lipophilic compounds such as DDT and progesterone to a lesser extent than hydrophilic compounds, such as benzoic acid, because the epidermal layer may not serve as the rate-limiting barrier for the diffusion of lipophilic compounds across the skin. Absorption into the circulation takes place at the dermal-epidermal boundary in vivo so the penetrant reaches the capillaries prior to traversing the dermis, hence the dermis does not act as a significant barrier to penetration. This is illustrated in Table 3-6.

Table 3-6. Influence of the Epidermis on Percutaneous Absorption of Compounds Through Pig Skin

		Percent Absorbed		
Compound	Log $K_{o/w}$	Epidermis Present	Epidermis Removed	Ratio
Benzoic acid	1.95	15 ± 4	88 ± 9	5.9
Testosterone	3.31	4 ± 2	15 ± 8	3.8
Progesterone	3.78	1.7 ± 0.6	7 ± 5	4.1
DDT	5.0	0.7 ± 0.3	1.2 ± 0.5	1.7

Source: Hawkins and Reifenrath (1986)

Skin Viability

The third of Tregear's (1966) assumptions regarding the use of excised skin in an in vitro diffusion study is that no living process affects permeability. However, Chapter 3 outlines the xenobiotic metabolizing capacity of the skin, and how metabolism may affect both the rate and amount of percutaneous absorption. Nevertheless, in vitro percutaneous absorption studies do not always consider skin viability and metabolic capacity and, in fact, may involve previously frozen skin. The influence of metabolic capacity effects on skin penetration needs further study, but for our purposes, they may be small with regard to cutaneous exposure assessment. Exploratory studies (Hawkins and Reifenrath, 1986) suggest that the metabolite capacity of mouse skin (CH3 strain) is much greater than that of swine or human skin.

Hawkins and Reifenrath (1984) measured the absorption of N,N-diethyl-m-toluamide (m-DEET) in full-thickness pig skin used immediately after excision and in pig skin stored for a period of 1 to 6 weeks at -80°C. Absorption of this compound through the frozen skin samples increased as a function of storage time. However, the authors of the two studies (Bronaugh et al., 1986b and DelTerzo et al., 1986) reported that freezing of the skin used in their studies had no effect on the integrity of these preparations or subsequent permeation of the topically applied compounds. Nevertheless, freezing the skin may affect the biotransformation of compounds that can be metabolized by the skin. For example, Holland et al. (1984) have shown that TCDD-induced BaP metabolism is markedly reduced by freezing mouse skin prior to in vitro use.

Collier et al. (1989a) described a method for maintaining the viability of skin in a flow-through diffusion cell for at least 24 hours using hepes-buffered Hank's balanced salt solution HHBSS as the receptor fluid. Viability was assessed by monitoring glucose utilization, metabolism of test compounds, and by electron microscopy. A complete tissue culture medium is not required to maintain viability of skin. The simplified balanced salt solution is less expensive and less likely to interfere with analytical techniques. Kao et al. (1984) developed a "static" system for simultaneously maintaining tissue viability and measuring in vitro percutaneous absorption. Researchers in this laboratory (Holland et al., 1984) have also developed a "dynamic" culture system. This system consists of a water-jacketed multisample skin penetration chamber, continuously perfused with oxygenated culture medium. This system not only provides the excised skin with an oxygen-rich tissue culture medium, but it also serves as a flow-through diffusion chamber for permeability studies. Franz et al. (1990) have recently used this system to measure the percutaneous penetration and chemical transformation of acetone-deposited organic solids.

3.2.2. Isolated Perfused Tubed-Skin Preparation

To overcome the potential limitations posed by in vitro systems, Riviere et al. (1985, 1986) used viable, isolated perfused tubed-skin preparations for determining in vitro percutaneous absorption rates. This system, an isolated perfused porcine skin flap (IPPSF), is viable for at least 10 hours. The tubed flap is transferred to an isolated organ perfusion apparatus (Figure 3-1).

This IPPSF preparation may be valuable to quantify the rate and degree of first-pass cutaneous metabolism of percutaneously absorbed xenobiotics without the confounding effects of biotransformation of the compound in other metabolically active tissues. It also permits percutaneous absorption to be modeled as a function of applied dose and cutaneous blood flow. Although the

IPPSF preparation shows potential for generating information useful for human exposure/risk assessment, its use is rather limited now.

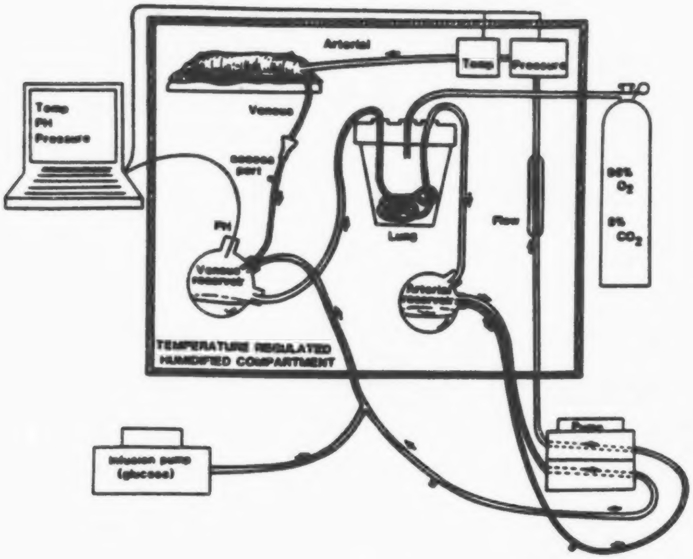
Arterial
Temp
Pressure
Temp
PH
Pressure
Venous
sample port
PH
Venous reservoir
Lung
Flow
95% O$_2$
5% CO$_2$
Arterial reservoir
TEMPERATURE REGULATED
HUMIDIFIED COMPARTMENT
Infusion pump (glucose)
Pump

Figure 3-1. IPPSF preparation and perfusion system.
Source: Riviere et al. (1985, 1986)

3.2.3. Stratum Corneum Binding Technique

Wester et al. (1987) have proposed an in vitro method to estimate the percutaneous absorption of chemical contaminants in aqueous solution based on the binding of these compounds to powdered stratum corneum. The method needs to be validated.

The stratum corneum binding technique was not used to obtain permeability values considered in this document. However, Wester et al. (1987) used the stratum corneum binding data to estimate the dose of *p*-nitroaniline that would be absorbed from water after bathing or swimming for 30 minutes. Caution should be exercised in using stratum corneum binding data for this purpose.

3.3. COMPARISON OF IN VITRO AND IN VIVO PERCUTANEOUS ABSORPTION VALUES

Parallel studies of in vitro and in vivo percutaneous absorption have been compared by Franz (1975, 1978). The in vitro percutaneous absorption of 12 organic compounds was evaluated using previously frozen, full-thickness human abdominal skin that was compared with the in vivo percutaneous absorption values obtained by Feldman and Maibach (1970). Although some in vitro and in vivo values did not agree quantitatively, Franz (1978) conducted modified tests with four compounds, as shown in Table 3-7. The technique was able to distinguish compounds of low permeability from those of high permeability, and the correlation showed fairly good agreement (Franz, 1978). Skin viability and receptor fluid compatibility were not taken into consideration.

Table 3-7. Total Absorption of Various Compounds by Skin In Vivo and In Vitro (Modified Tests) (Expressed as Percent of Applied Dose)

Compound	Absorption In Vivo[a]	T[b]	Absorption In Vitro[a]
Nicotinic acid	0.32 ± 0.10 (3)	21	2.3 ± 0.9 (4)
Hippuric acid	1.0 ± 0.4 (6)	3	1.25 ± 0.5 (4)
Thiourea	3.7 ± 1.3 (4)	21	4.6 ± 2.3 (5)
Caffeine	22.1 ± 15.8 (4)	7	24.1 ± 7.8 (4)

[a] Mean ± standard deviation; the values in brackets represent the number of subjects studied.
[b] Number of days urine was collected.

Source: Franz (1978)

Reasonably good agreements of in vitro and in vivo percutaneous absorption data have been obtained for relatively hydrophilic compounds using a standard diffusion cell technique. For example, the percent absorption of benzoic acid measured in vivo (42.6%) by Feldman and Maibach (1970) was similar to the value obtained with the static in vitro diffusion cell (44.9%) (Franz, 1975). Bronaugh et al. (1982a) also reported good agreement between in vitro and in vivo values for another relatively hydrophilic compound, acetylsalicylic acid.

Investigators have had difficulty predicting the in vivo percutaneous absorption of lipophilic compounds by using in vitro techniques. Although further research is needed, these limitations have been improved by major modifications in the standard diffusion cell technique proposed by Bronaugh and Stewart (1984):

- Use of a split-thickness skin preparation in which the dermis is markedly reduced or completely removed; and
- Use of receptor fluids that provide a greater solubility for the permeant than saline.

The use of a flow-through receptor medium fluid compartment to provide a greater volume of receptor media has also been shown to improve the predictive capability of in vitro percutaneous absorption studies. The capability of these modifications to improve the predictive capability of in vitro percutaneous absorption studies has been documented in previous sections of this chapter.

For example, the in vivo percutaneous absorption of the relatively lipophilic compounds DDT and Fenvalerate can be closely approximated when split-thickness in vitro skin preparations are used. However, the results obtained by using full-thickness preparations are quite different from those measured in vivo (Grissom et al., 1987). Recognition of the poor diffusion of lipophilic compounds through the relatively aqueous dermis and of the insolubility of these compounds in a static aqueous receptor fluid has led to the increased use of split-thickness skin preparations and compatible receptor media or flow-through diffusion cells to measure the in vitro percutaneous absorption of lipophilic compounds.

Differences in the degree of in vitro and in vivo percutaneous absorption may be a function of the time at which these measurements were taken. Yang and colleagues have shown that for anthracene (Yang et al., 1986a) and BaP (Yang et al., 1986b) the total amounts of absorption measured in vitro and in vivo are somewhat different when measured at day 1 or 2 of a 5-day study, but they do coalesce over time. These investigators have attributed the greater differences observed at earlier time points to the systemic uptake, metabolism, and elimination of the compound that occurs in vivo. This results in a time delay between absorption of the compound across the stratum corneum and measurement of the compound or metabolites in exhaled air or excreta. The time that it takes for these processes to occur accounts for the apparent lag in the in vivo results. Yang and coworkers (1986b) have speculated that the coalescence of the in vitro and in vivo values over time occurs because "lag time" becomes less of a factor in the determination of cumulative recovery of absorbed BaP in vivo.

In summary, in vitro percutaneous absorption values are generally good predictors of the rate or extent of percutaneous absorption that occurs in the intact animal. However, the factors described in the previous sections of this chapter may affect the predictive accuracy of in vitro percutaneous absorption, especially for compounds that are neither very hydrophilic nor very lipophilic. In many cases, failure to control for these variables will lead to a poor correlation between in vitro and in vivo percutaneous absorption values. Therefore, if in vitro K_p data are used to estimate percutaneously absorbed data, the exposure/risk assessor should examine the conditions under which the in vitro percutaneous absorption study was conducted, to determine how well the in vitro K_p can be expected to approximate the results obtained in vivo.

3.4. INTERSPECIES COMPARISON OF PERCUTANEOUS ABSORPTION VALUES

Percutaneous absorption studies in which the compound is applied to human skin in vivo provide the most relevant information for human exposure/risk assessment. However, the toxicity of many compounds of interest to exposure/risk assessors limits their testing in humans in vivo. Alternatively, data from studies using experimental animals or in vitro techniques provides the K_p data necessary for estimating percutaneously absorbed dose in humans.

Examination of the K_p values considered in this document reveals that the majority of these values were obtained in studies in which the compound was applied in vivo or in vitro to the rat skin. The advantages of using this species to obtain percutaneous absorption rate data have been reviewed by Zendzian (1989). For example, these animals are readily available to the research community; have a defined genetic background, thereby minimizing the degree of individual variation in handling xenobiotic compounds; and have a surface area sufficient for dose application. However, rat skin, as well as skin from the mouse, rabbit, or guinea pig have consistently been shown to be more permeable to topically applied compounds than human skin. Furthermore, the male rat differs from the female rat in skin permeability of the dorsal skin.

Wester and Maibach (1986) summarized the results of several investigators who ranked, from highest to lowest, the relative in vitro percutaneous absorption of different species, as shown in Table 3-8.

Table 3-8. Ranking of the Relative In Vitro Percutaneous Absorption of Different Species

Tregear (1966)	Marzulli et al. (1969)	McGreesh (1965)
Rabbit	Mouse	Rabbit
Rat	Guinea Pig	Rat
Guinea pig	Goat	Guinea pig
Human	Rabbit	Cat
	Horse	Goat
	Cat	Monkey
	Dog	Dog
	Monkey	Pig
	Weanling pig	
	Man	
	Chimpanzee	

[a] Based on studies involving organophosphate compounds.

Source: Wester and Maibach (1986)

To use percutaneous absorption rates obtained from animal studies in exposure/risk assessment, it would be useful to understand how rat, mouse, rabbit, guinea pig, and human skin compare. Bronaugh et al. (1982b) summarized some of these data in Table 3-9.

Table 3-9. Permeability of Animal Skin Relative to Human Skin[a,b]

Reference and Compound	Log $K_{o/w}$	Pig	Rat	Guinea Pig	Hairless Mouse	Mouse	Rabbit
Tregear (1966)							
Ethylenebromide	1.96	0.8	2.3	1.5			
Paraoxon	—	1.4	3.3	3.0			
Thioglycolic acid	0.09	3.3	3.0	2.3			
Water	-1.38	1.4		1.0			3.3
Chowhan and Pritchard (1978)							
Naproxin	—	2.3					3.5
Durrheim et al. (1980)							
Butanol	0.65	1.8					
Ethanol	-0.31	1.5					
Octanol	2.97	0.6					
Stoughton (1975)							
Betamethasone	—		1.3				
5-Fluorouracil	-0.95	1.1					
Hydrocortisone	1.61		1.5				
Bronaugh et al. (1982b)							
Acetylsalicylic acid	1.19	1.2	1.0		4.9	8.7	
Benzoic acid	1.87	0.2	0.6		2.0	2.0	
Urea	-2.11	1.5	4.8	0.9	5.8		

[a] Values for human skin in all studies were assigned a value of 1.0.

[b] All values are based on in vitro determinations.

Source: Bronaugh et al. (1982b) for permeability data; Hansch and Leo Log P database (1979) for Log $K_{o/w}$ data.

Other investigators also demonstrated the similarity in the relative permeabilities of human and pig skin for compounds with a range of log $K_{o/w}$ values using in vitro studies (Hawkins and Reifenrath, 1986). Monkey skin has been shown to be a good model for human skin in a number of in vitro studies. Bronaugh and Maibach (1985) found the in vitro percutaneous absorption of nitroaromatic compounds to be similar in human and monkey skin, as shown in Table 3-10, but the excised human skin tended to be somewhat less permeable.

Table 3-10. Percutaneous Absorption of Nitroaromatic Compounds in Human and Monkey Skin[a]

		Applied Dose (%)	
Compound	Log $K_{o/w}$	Human	Monkey
p-Nitroaniline	1.39	48.0 ± 11.0	62.2 ± 6.1
p-Amino-2-nitrophenol	0.96	45.1 ± 8.0	48.2 ± 7.8
2,4-Dinitrochlorobenzene	1.90	32.5 ± 8.7	48.4 ± 3.9
2-Nitro-p-phenylenediamine	0.53	21.7 ± 2.6	29.6 ± 4.3
Nitrobenzene	1.85	7.8 ± 1.2	6.2 ± 1.0

[a] Based on in vitro studies.

Source: Bronaugh and Maibach (1985)

Walker et al. (1983) compared the relative in vitro percutaneous absorption rates of water and paraquat through excised human and experimental animal skin. As shown in Table 3-11, the absorption rates of water in the excised hairless rat and hairless mouse skin are about 1.5- to threefold greater, respectively, than in human skin; K_p values measured in rabbit and guinea pig skin were about three- to fivefold greater, respectively, than human skin. However, the K_p values for paraquat obtained for all animal models were markedly greater than those of humans, ranging from 40-fold greater for the rat to 1,500-fold greater for the hairless mouse.

Several trends are evident from the data presented in Tables 3-8 through 3-11. The percutaneous absorption of many compounds in the pig and monkey is similar to that found in humans. However, although rat, mouse, rabbit, or guinea pig skin may be useful models for human skin, they may overestimate percutaneous absorption in humans. Therefore, the use of percutaneous absorption values obtained in experimental animal studies will almost always result in a conservative (i.e., higher) estimate of percutaneously absorbed dose in humans.

Table 3-11. Relative In Vitro Percutaneous Absorption of Water and Paraquat Through Human and Animal Skin

	Permeability constant (x 10^{-5} cm/hr)	
	Water	Paraquat
Human	93	0.7
Rat	103	27.2
Hairless Rat	130	35.3
Nude Rat	152	35.3
Mouse	164	97.2
Hairless Mouse	254	1065.0
Rabbit	253	92.9
Guinea Pig	442	196.0

Source: Walker et al. (1983)

The variability in estimates of animal skin permeability relative to that of human skin makes it difficult to suggest a factor to correct for the increased permeability of animal skin when using these values in a human exposure/risk assessment. Vanderslice and Ohanian (R.R. Vanderslice and E.V. Ohanian. Dermal absorption of drinking water contaminents, presented at the Society of Toxicology Meeting in Atlanta, GA, 1989) observed from the data reported from Scheuplein and Blank (1973) and Flynn et al. (1980), that a fivefold difference in the percutaneous absorption rate of a series of alkanols exists in excised human and mouse skin, respectively. Based on this observation, they adjusted the K_p values obtained in mice or rats by a factor of 5 to approximate human absorption rates.

In addition, McDougal et al. (1990) observed, on average, a two- to threefold difference in the K_p of chemical vapors between rat and human skin. Therefore, from these observations and the relative permeabilities summarized in Table 3-9, it may be reasonable to correct the percutaneous absorption rates from mouse and rat studies by a factor of 3 to 5 to obtain more realistic estimates of human K_p values. However, the relatively small database, currently available, makes it difficult to validate this approach for environmental pollutants.

In summary, the permeability values considered in this document have been obtained by a variety of techniques. Before using these values to estimate the percutaneously absorbed dose of environmental pollutants in humans, the exposure/risk assessor should be aware of the limitations of the technique used. In addition, if the value comes from either an in vitro or experimental animal study, the exposure/risk assessor should explain how this value might approximate the values expected for human skin in vivo. General guidance on the evaluation of these factors has been presented in this chapter, and is summarized in Table 3-12.

3.5. SUMMARY, CONCLUSIONS, AND RESEARCH RECOMMENDATIONS

A permeability constant is a convenient way of expressing skin permeation rates since, by definition, absorption rate is directly proportional to concentration. However, K_p values can only be calculated from steady-state absorption rates which usually occur only after prolonged exposure (minutes to hours) to an infinite dose. Calculation of exposure to aqueous solutions of chemicals during swimming and bathing are instances where permeability constants can be used to approximate percutaneous absorption. The evaluation of techniques for measuring dermal absorption reflects the specific requirements for measuring steady-state rates of skin permeation after exposure to aqueous solutions. The in vivo and in vitro procedures can also be used to measure percutaneous absorption following topical application of compounds mixed with soil.

Table 3-12. Summary of Factors That May Affect the Use of K_p Data in Cutaneous Exposure Assessment

	Factor	Comments
1.	Type of Study Used to Obtain Data	
	In Vivo/Radioactivity	May not represent absorption of the parent compound.
	In Vivo/Parent or Metabolite	Sensitive assay is often needed to detect parent compound. One needs to know the pharmacokinetic behavior of the compound if metabolite data are used.
	In Vivo/Biological Response	Response may indicate absorption and potency of the compound. May not be quantitative.
	In Vivo/Stripping	No data considered in this document used this method.
	In Vivo/Disappearance	Used to provide K_p data for key environmental compounds, but may measure both absorption and binding in stratum corneum. Evaporative loss may confound findings.
	In Vitro/Diffusion Cell	Commonly used technique to provide K_p values. Need to examine the conditions of the study to determine how they may have affected the results. Consider species differences and lipophilicity of test materials.
	In Vitro/IPPSF	New technique; shows promise, but little available data.
	In Vitro/Stratum Corneum Binding	Shows promise, but not well validated.
2.	In Vitro to In Vivo Comparison of Percutaneous Absorption Values	In vitro results are often good predictors of in vivo data; however, one needs to carefully examine the conditions under which the in vitro studies were conducted. Species and lipophilicity affect results.
3.	Interspecies Comparison of Percutaneous Absorption Values	Percutaneous absorption values obtained using monkey or pig skin often approximate values obtained in humans. Rat, rabbit, mouse, and guinea pig skins are generally five to ten times more permeable than human skin.

In vivo absorption methods give "physiological" measurement of absorption. Rates of permeation of chemicals (for example, $\mu g/cm^2$-hour) cannot be precisely measured by analysis of absorbed material in excreta, therefore permeability constants are difficult to determine by those in vivo techniques. In some cases in vivo measurements can be improved by sampling from blood and by pharmacokinetic analysis. Possibility for error exists in correcting for incomplete excretion, particularly for lipophilic compounds that can remain in the body for days or even weeks. Analysis of absorbed material in the body tissue as well as the excreta provides more complete information but requires sacrifice of test subjects at each timepoint of the absorption measurement.

In vitro absorption methods give easily obtainable rate measurements for skin permeation from which permeability constants can be determined. Data for human skin can be obtained even for toxic chemicals. Skin metabolism can be observed without interference from systemic effects. Care must be taken to accurately simulate in vivo conditions since many variables must be considered (preparation of membrane, type of diffusion cell, receptor fluid, temperature, etc.). Lipophilic compounds absorbed into skin may not partition freely into the receptor fluid. Material in skin must be included with that found in the receptor fluid for determination of total percutaneous absorption. Use of surfactants or other lipophilic receptor fluids abolish metabolic activity in skin. They should only be used under conditions that have been demonstrated to be without effect on barrier properties of skin.

In vivo - in vitro comparisons: Many comparisons have been made with reasonable agreement in skin permeation values usually obtained. When agreement between methods is not obtained, methodological problems or differences in the in vivo and in vitro test systems may be responsible. Resolution of these problems should facilitate good comparability of absorption data.

Interspecies comparison of absorption data: Human skin is generally a better barrier to absorption of chemicals than animal skin. Mouse and rabbit skin have the poorest barrier properties of commonly used animal models. Monkey, pig, guinea pig, and rat have skin generally more permeable than human skin, but with some compounds (especially when using monkey and pig skin), the differences are small. The numerical differences between human and animal skin permeability values vary with the test compound. Because of the uncertain extent of enhanced permeation through animal skin, it may be best to simply consider animal data as a conservative estimate of human absorption and not attempt to arbitrarily convert it to human data by dividing by a factor such as 3, 5, etc.

The research needs in this area are summarized below:

- Further data are needed to establish the relationship between in vivo and in vitro percutaneous absorption measurements for compounds in environmental media. Variables could include: dose dependency of absorption, absorption of mixtures, evaporation of chemicals following in vivo and in vitro application.
- Additional studies are needed to assess the importance of skin metabolism in percutaneous absorption and to compare skin metabolism in human and animal skin. Effects of varying chemical dose on metabolism in skin should be examined.
- The role of cultured human epidermal membranes should be examined for use in skin absorption/metabolism studies.
- The use of physiologically based pharmacokinetic models should be studied for possible use in estimation of target organ concentration and in predicting species differences in absorption and metabolism.
- Studies should be conducted to clarify issues relating to mechanisms of percutaneous absorption. Uncertainties remain in the role of appendages, the vascular system, and dermal tissue in skin permeation studies.

4. MATHEMATICAL DESCRIPTION OF DERMAL ABSORPTION

The dose absorbed per event (DA_{event}, unit in mg/cm^2-event) can be estimated from one of the following approaches:

- Permeability coefficient ($K_{p,s}$) - A flux value, normalized for concentration, that represents the rate at which the chemical penetrates the skin (cm/hour). This document uses the convention that the second subscript designates the membrane of interest, e.g., (s) for skin, (m) for membrane, etc.
- Percent absorbed - The percentage (%) or fraction of the applied dose absorbed across the skin in a specified time. In order to be meaningful, the duration of exposure or decontamination time and observation time should be indicated along with amount applied per unit area and the area exposed.

When Fick's first law prevails under steady-state conditions, the permeability coefficient can be evaluated from the measured steady-state flux (J_{ss}) through the skin as long as the concentration differential across the skin is known, or, under some circumstances, it can be roughly approximated from the percent of the compound absorbed. Since experimental conditions vary greatly among in vitro studies, and between in vitro and in vivo systems, estimation of the permeability coefficient from measured flux or percent absorbed is not always possible.

Dermal absorption from both in vitro and in vivo studies is often reported as percent absorbed in order to simplify data collection and analysis. However, as reported in the literature, the percent absorbed is not an independent constant to be applied indiscriminately to any exposure scenario. The percent absorbed implicitly contains several experimental conditions, including the exposure period, the concentration, and the dose used in the studies, and therefore can vary greatly from study to study even for the same chemical.

Currently, the percent absorbed is used to estimate the dose resulting from contact with soil. This approach may be practical if the amount of contaminant in the adhered soil can be established accurately. However, not all of the soil contaminant in a thick layer of soil applied to the skin can be considered to be bioavailable. The percentage of the initial dose absorbed is rarely measured at steady-state and is generally given as a proportion of the applied dose that is absorbed (or lost from the application site) after a contact duration or at various time steps during such contact.

Furthermore, the percent absorbed is dependent upon the amount applied per unit area and decreases with increasing amount applied. The significance of this measure of dermal absorption is that the percentage of the dose absorbed after 1 hour would not necessarily be the same as the percentage absorbed after 24 hours, nor is it equivalent to 1/24 the percentage absorbed after 24 hours.

For water or vapor scenarios, it is not practical to apply this concept of percent absorbed because of the difficulty in estimating the contact rate. Attempts have been made to apply dermal absorption models that consider the thickness of a thin film of chemical and water on the skin (EPA, 1983; Wester et al., 1987; Wester and Maibach, 1989b). However, for exposure scenarios of interest in environmental settings, this thickness is difficult to establish. There is essentially an infinite thickness of material available, and the contaminant will be continuously replaced, thereby increasing the amount of available material by some large, but unknown, amount.

In contrast, flux (J_{ss}) and permeability coefficient ($K_{p,s}$) values are generally determined under conditions of steady-state, or near steady-state. Additionally, when Fick's first law of diffusion is applicable (i.e., no chemical-related skin damage), the permeability coefficient is constant over the range of contaminant concentrations generally of interest. This provides a much more consistent basis for comparing the dermal absorption potential of chemicals of concern.

Therefore, the permeability coefficient-based approach is advocated over the absorption fraction approach for determining the dermally absorbed dose of compounds in an aqueous media or air. Because of the lack of data demonstrating the scientific reliability of using aqueous $K_{p,s}$ data for compounds bound to soil and reduced uncertainty in defining an applied dose, the absorption fraction-based approach is presently recommended for determining the dermally absorbed dose of soil contaminants.

The following section presents the general description of Fick's first law and the assumptions underlying the application of this equation in the evaluation of permeability coefficients from experimental data. In the simple case of the in vitro experimental system of the diffusion cell where Fick's first law holds, the evaluation of $K_{p,s}$ from J_{ss} is described. A brief description of in vivo percutaneous absorption measurement is then provided, with some discussion of a possible equivalent in vivo "permeability coefficient."

4.1. THEORETICAL BASIS OF K_P AND J_{SS} VALUES

Fick's first law of diffusion is used to relate the steady-state flux J_{ss} of a compound through the membrane to the concentration differential (Δ C) across the membrane, as shown in Equation (4.1). The proportionality constant is called the permeability coefficient ($K_{p,m}$).

$$J_{ss} = K_{p,m} \, \Delta \, C \qquad (4.1)$$

The use of this simple flux equation requires that steady-state diffusion occurs uni-dimensionally, and that there is no convection in the direction of the uni-dimensional diffusion. Applying Fick's first law to diffusion across any membrane, the steady-state assumption implies that, physically, the volumes of the solutions adjacent to the two sides of the membrane must be much greater than the effective volume of the membrane (taking actual distribution into account), that these solutions are well-mixed, and that the concentration of the compound at the membrane's surface is constant. The concentration difference is measured on the upstream and downstream faces of the membrane.

A membrane is chemically distinct and separate from the external solutions. For a molecule to pass from one side of the membrane to the other, it must partition into the membrane and then migrate across the full thickness of this membrane. Thus, the permeability coefficient is a function of the path length of chemical diffusion (l_m), the membrane/vehicle partition coefficient ($K_{m/v}$) of the chemical, and the diffusion coefficient (D_m) of the chemical in the membrane, and can be written for a simple isotropic membrane as:

$$K_{p,m} = \frac{K_{m/v} \, D_m}{l_m} \qquad (4.2)$$

However, time is usually required after initial contact with the skin for such a steady-state to be achieved. This unsteady-state period is a function of the lag time (τ), which is defined for a simple, isotropic membrane as (Crank, 1975; Scheuplein and Blank, 1971):

$$\tau = \frac{l_m^2}{6D_m} \tag{4.3}$$

Comparable parameters function for labyrinthine membranes like the skin, although in this case, $K_{p,s}$, $K_{s/v}$, D_s, and l_s generally defy true assessment as a result of the complexities. It is still useful, however, to think of $K_{p,s}$ in terms of partitioning, molecular mobility, and path length. $K_{p,s}$ is an experimental parameter that is valid as long as the above-stated assumptions are met.

On combining Equations (4.1) and (4.2), an expanded expression for flux across the skin is obtained:

$$J_{ss} = \frac{K_{s/v}\, D_s\, \Delta C}{l_s} \tag{4.4}$$

If we limit our discussion and stipulate that the stratum corneum is the rate-limiting membrane of the skin, then the following assumptions, employed by Blank (1964) and Scheuplein (1965), are necessary for Equation (4.4) to be strictly valid:

- The full thickness of the stratum corneum contributes to the diffusion barrier;
- No active transport occurs;
- The stratum corneum is a homogeneous medium;
- Penetrant and vehicle molecules diffuse across the stratum corneum as individual entities; i.e., there is no carrier effect;
- There are no size-limiting pores to affect absorption;
- The stratum corneum is not changed progressively by the vehicle or penetrant; and
- Penetrant concentration changes do not alter stratum corneum or vehicle properties.

Some of these assumptions are considerable and may be questioned. One must use Equation (4.4) with the realization that $K_{p,s}$, the experimentally derived parameter, may not conform to the simple relationship defined in Equation (4.2) for the simple homogeneous membrane. Equation (4.1) is nevertheless, useful for the estimation of $K_{p,s}$ from experimentally measured J_{ss} values. Equation (4.4) is of conceptual utility in that it relates the function of the barrier to the partitioning, molecular mobility, and path length factors. With the assumption that the stratum corneum provides the limiting barrier to skin penetration, Equations (4.1) through (4.4) can be redefined in terms of $K_{p,sc}$, $K_{sc,v}$, D_{sc}, and l_{sc}.

In Section 4.2., the effects of these key parameters on the percutaneous flux are discussed theoretically. The experimental measurement of $K_{p,sc}$ is discussed in Section 4.3.

4.2. DERMAL (PERCUTANEOUS) ABSORPTION RATE EQUATION PARAMETERS

4.2.1. Partition Coefficient

The partition coefficient $K_{sc/v}$ defines the equilibrium ratio of the concentration of the compound in the stratum corneum to that in the adjacent solution (vehicle). By using $K_{sc/v}$ in Equation (4.2), it is assumed that attainment of equilibrium at the stratum corneum-vehicle interface is rapid, meaning the thermodynamic activity of the permeant at the stratum corneum's surface is virtually equivalent to that in the adjacent bulk solution.

The determination of $K_{sc/v}$ values as described by Scheuplein (1965) involves:

- Allowing a known quantity of dry stratum corneum to equilibrate with a solution of known concentration of the compound under study;
- Determining the concentration of the compound in the solution after equilibrium is reached; and
- Using the difference between the initial and final solution concentrations to determine the amount of the compound partitioned into the stratum corneum.

The partition coefficient is then determined by:

$$K_{sc/v} = \frac{\textit{Concentration in the stratum corneum}}{\textit{Concentration in the vehicle}} \tag{4.5}$$

Durrheim et al. (1980) restated Equation (4.5) as:

$$K_{sc/w} = \frac{(C_o - C_e) \; / \; V_{sc}}{C_e / V_w} \tag{4.6}$$

where C_o and C_e are the initial and equilibrium concentrations of the chemical in the aqueous phase, V_{sc} is the volume of stratum corneum used, and V_w is the aqueous solution volume.

Several investigators have developed modifications to this approach. For example, Bronaugh et al. (1981) enclosed dried, weighed pieces of stratum corneum in filter paper (to facilitate removal of the tissue) and exposed the tissue to various vehicles containing ^{14}C-N-nitrosodiethanol- amine (NDELA). Once the stratum corneum was removed, dried, and reweighed, the content of ^{14}C-NDELA in the stratum corneum was determined by liquid scintillation counting. The partition coefficient was then estimated according to Equatiou (4.6). Other, more recent reports (Raykar et al., 1988; Anderson et al., 1988; Surber et al., 1990a,b) have also described approaches to the measurement of $K_{sc/v}$ values. Measured for water, $K_{sc/w}$ values should reflect the absorptive capacity of the stratum corneum as set out in Equation (4.6).

Difficulty with the basic estimation approach outlined above arises when the exposure involves a chemical dissolved in a nonaqueous vehicle. The flux calculation now requires knowledge of the stratum corneum/vehicle partition coefficient. The latter may be awkward to measure, particularly if the vehicle is an organic solvent that can alter the solvency of the stratum corneum. There have been attempts to evaluate stratum corneum/vehicle $K_{sc/v}$ values when the vehicles used were nonaqueous. For example, Blank and McAuliffe (1985) proposed a method to evaluate the $K_{sc/v}$ of benzene from gasoline. More recently, Surber et al. (1990a,b) reported stratum corneum/isopropyl myristate partition coefficients, $K_{sc/ipm}$, for a series of compounds, and showed the anticipated relationship between the three possible partition coefficients of a chemical present in three different phases, namely:

$$K_{13} = K_{12}/K_{32} \tag{4.7}$$

holds reasonably well. In Equation (4.7), we might equate K_{12} and K_{32} with a chemical's partition coefficient between (a) stratum corneum and water (K_{12}), and (b) an organic solvent and water (K_{32}). It follows that K_{13} is the chemical's predicted partition coefficient between stratum corneum and the organic solvent. In this way, if K_p^w of the chemical from water is known, the corresponding value from the organic solvent may be estimated by an appropriate correction using the chemical's organic solvent/water partition coefficient (which is easily determined by experiments for water immiscible solvents).

Perhaps a more satisfying, experimental solution to the problem of partitioning from different vehicles is obtained by ascertaining fluxes from saturated solutions. Barring supersaturation, the maximum possible flux of a chemical across a membrane (J_{max}) is given by:

$$J_{max} = \frac{D_m}{l_m} \cdot C_m^{sat} \tag{4.8}$$

where C_m^{sat} is the saturation solubility of the chemical in the membrane. If solubilities are modest, it is also true that the membrane/water partition coefficient ($K_{m/w}$) of the chemical can be defined as:

$$K_{m/w} = \frac{C_m^{sat}}{C_w^{sat}} \tag{4.9}$$

where C_w^{sat} is the saturation solubility of the chemical in water.

Combining Equations (4.8) and (4.9) gives:

$$J_{\max} = \frac{K_{m/w}\, D_m}{l_m} \cdot C_w^{sat} \tag{4.10}$$

$$= K_p^{\,w} \cdot C_w^{sat} \tag{4.11}$$

If the chemical contacts the skin from an organic solvent (subscript os), which does not alter appreciably the barrier properties, then the equivalent equations to (4.9) and (4.10) are:

$$K_{m/os} = \frac{C_m^{sat}}{C_{os}^{sat}} \tag{4.12}$$

and

$$J_{\max} = \frac{K_{m/os}\, D_m}{l_m} \cdot C_{os}^{sat} \tag{4.13}$$

If we rewrite $K_{m/os}\ C_{os}^{sat}$ in Equation (4.13) as C_m^{sat} (as indicated by Equation [4.12]), then Equation (4.13) reduces to the basic statement of Fick's first law (Equation 4.8). It follows, therefore, that if the membrane is unaffected by the vehicle, the J_{max} of chemical applied as a saturated solution will be independent of the solvent. In this way, if one knows the degree of saturation of the chemical in the applied phase, then one can calculate the fraction of the maximum possible flux across the membrane. The issue of exposure to chemicals in non-aqueous media and the corresponding definitions of appropriate permeability coefficients are revisited below.

It must be stressed, however, that the validity of the preceding argument, which is based on purely thermodynamic principles, requires that the interaction of the vehicles with the stratum corneum be negligible. This is ordinarily not the case, and it is very difficult, therefore, to predict the penetration of a chemical applied as a neat liquid from its permeability coefficient determined following topical administration in an aqueous solution. Results for benzene illustrate this point rather well (Blank and McAuliffe, 1985). Similarly, the form of the relationship describing the dependence of the permeability coefficient upon a particular physico-chemical parameter (e.g., an oil/water partition coefficient) will be significantly affected by the conditions under which it is measured. This can be illustrated by the permeability coefficient values of the n-alkanols applied as either aqueous solutions or neat liquids (Idson and Behl, 1987), and by the more recent data of Dal Pozzo et al. (1991) using nicotine acid derivatives.

In general, stratum corneum/water partition coefficient values are rarely reported in the literature. In the absence of experimentally derived $K_{sc/w}$ values, one can approximate $K_{sc/w}$ values for nonelectrolytes in an aqueous solution using the octanol/water partition coefficient ($K_{o/w}$). For example, Roberts et al. (1977) proposed the following empirical relationship for phenolic compounds and aromatic alcohols:

$$\log K_{sc/w} = 0.5 \log K_{o/w} - 0.1 \qquad (4.14)$$

Octanol/water partition coefficient values for a large number of compounds have been compiled by Hansch and Leo (1979) and are also reported in EPA documents such as the Superfund Exposure Assessment Manual (EPA, 1988b).

4.2.2. Pathlength of Chemical Diffusion

The diffusion path length (ℓ_{sc}) is assumed to be equal to the thickness of the stratum corneum, i.e., 10-40 μm (although stratum corneum thickness can be much greater on certain sites of the body, such as the palms and soles). However, there is increasing acceptance that permeants spanning a very diverse range of physico-chemical properties move through the stratum corneum via a tortuous pathway confined to the intercellular lipid channels. Such a pathway has been estimated to have a diffusion path length of several hundred μm (Albery and Hadgraft, 1979; Michaels et al., 1975; Potts and Francoeur, 1991).

4.2.3. Diffusion Coefficient

The other key parameter that determines the permeability coefficient and the flux is the diffusion coefficient. Most diffusion coefficients of relatively small ($<$ 500 D_a) nonelectrolytes in water and in light organic liquids are on the order of 10^{-5} cm^2/second to 10^{-6} cm^2/second at 25°C (Cussler, 1984). For high-molecular weight solutes, e.g., albumin and polystyrene, diffusion coefficients can be much smaller (10^{-7} to 10^{-8} cm^2/sec).

Apparent diffusion coefficients across the stratum corneum have been reported to be as small as 10^{-13} cm^2/sec (Scheuplein, 1965; Scheuplein and Blank, 1971; Kasting et al., 1987). These values suggest lag times of many days. The estimation of these diffusion coefficients is typically based upon Equation (4.4), assuming a diffusion path length l_{sc}, and given the measured lag time (τ). Alternatively, they are calculated from experimentally determined partition coefficients and permeability coefficients. Using Equation (4.4) and l_{sc} = 500 μm results in diffusion coefficients on the order of 10^{-7} to 10^{-9} cm^2/second. In addition, sorptive phenomena concomitant with transport delay the onset of steady-states (lengthen lagtimes). Whatever the true situation for a specific compound, the facts that (a) experimental determinations of $K_{sc/v}$ are difficult, and (b) lag-time measurements are notoriously imprecise, mean that we can rarely do better than evaluate the ratio of D_{sc} to l_{sc} or l_{sc}^2. There is so much uncertainty here that, in order to extrapolate from one chemical to another, it is more appropriate to assume that l_{sc} is the same for both compounds, and extrapolate based on a ratio of D_{sc} values, rather than to specify an "exact" value of D_{sc} (based on an assumed l_{sc}).

Because the diffusion of a solute in a solvent requires displacement of the solute through the continuum of solvent molecules, the ease of diffusion is inversely related to solute size (i.e., the D_{sc} of a large molecule is less than that of a smaller molecule). The dependence of D_{sc} on solute size (as measured by molecular weight or molecular volume) has been modeled in a number of ways. With respect to percutaneous absorption, Guy et al. (1985) used the Stokes-Einstein equation to relate the diffusion coefficients of two chemicals (A and B) to their respective molecular weights (MW_a and MW_b):

$$D_a = D_b \left[\frac{MW_b}{MW_a} \right]^{1/3} \tag{4.15}$$

Alternatively, Kasting et al. (1987) proposed a more severe exponential dependence:

$$D = D^o \cdot \exp(-\beta \cdot MV) \tag{4.16}$$

where D^o and β are constants, characteristic of the medium through which diffusion is occurring, and MV is the solute's molecular volume. Equations such as (4.15) and (4.16) can be used appropriately in methods to predict permeability coefficients and to interpret experimental data when permeability coefficient values have been measured for a diverse range of chemicals (see Chapter 5).

4.2.4. Concentration Gradient

There is every reason to believe that the removal of most compounds by capillaries in the dermal layer is efficient in normally functioning skin. When there are no blood flow limitations to the removal of penetrant compounds, given the massive volume of distribution of the body, the concentration of the chemical of interest at the point of capillary uptake is assumed to be zero. Therefore, the differential in concentration of solute across the membrane (ΔC) can be represented simply by the concentration of the solute in the vehicle, C_v, as shown in Equation (4.17). C_v is either set experimentally (diffusion cell studies), is measured (field studies), or is estimated for specific exposure scenarios.

$$\Delta C \approx C_v \tag{4.17}$$

4.3. EVALUATION OF PERMEABILITY COEFFICIENTS $K_{P,S}$ FROM EXPERIMENTAL STUDIES

Experimental values of permeability coefficients can be measured directly under in vitro conditions or evaluated indirectly from in vivo data by fitting the appropriate variable in pharmacokinetic models. Where data are lacking, $K_{p,s}$ can be estimated from appropriate physical property-permeability relationships (see Chapter 5).

4.3.1. In Vitro Approaches

As stated, the permeability coefficient is an experimentally measured parameter characterizing the total barrier property of a membrane. This is so irrespective of how complex or simple a membrane might be. Permeability coefficient values across the membrane can be accurately evaluated from specific in vitro diffusion cell studies using Fick's first law (Equation 4.1) with the aid of a two-chamber diffusion cell. The membrane is sandwiched between the application (donor) and collection (receptor, receiver) chambers. Both the donor and receptor compartments of the diffusion cell are filled with media, the former usually with a dilute aqueous solution of the permeant of interest, and the latter usually with a blank solvent (buffer, saline, etc.), although in principal any fixed but lower concentration of the permeant of interest could be used. Since the donor and receptor chambers are separated by the membrane, the solute diffuses from the fixed higher concentration medium in the donor chamber into the less concentrated solution in the receptor chamber. To determine the permeability coefficient of a solute, the concentrations in the donor and/or receptor compartments are measured as a function of time.

The main assumption of the diffusion cell experiment is that the flux across the membrane reaches its steady-state or quasi-steady-state value reasonably quickly. Steady-state is achieved when the concentrations in the donor and receiver chambers are constant with time, and the flux across the membrane is constant. Physically, this means that the volumes of the two chambers must be much greater than the volume of the membrane. More often, experiments are performed where slight decreases in the donor concentration take place with corresponding mass accumulations in the receptor compartment (Cussler, 1984). The concentrations of samples obtained from both donor and receptor compartments are measured as a function of time. By assuming that the flux across the diaphragm reaches its steady-state very quickly, despite the time dependence of the concentrations in the two chambers, the resulting pseudosteady-state flux across the membrane can be described by a form of Fick's first law of diffusion (Equation 4.1):

$$J_{ss} = K_p \cdot \left(C_{donor} - C_{receiver}\right) \tag{4.18}$$

Mass balance in the donor and receiver compartments requires that:

$$V_{donor} \frac{dC_{donor}}{dt} = -A\ J_{ss} \tag{4.19}$$

and

$$V_{receiver} \frac{dC_{receiver}}{dt} = A\ J_{ss} \tag{4.20}$$

where A is the surface area of the membrane.

If $V_{donor} = V_{receiver} = V$, and the concentrations C_{donor} and $C_{receiver}$ can be measured as a function of time, then the permeability coefficient K_p is given by:

$$K_p = \frac{(slope)\ (V/A)}{(C_{donor} - C_{receiver})} \tag{4.21}$$

where the slope equals the absolute value of $dC_{receiver}/dt$, the gradient of the linear part of the plot of $C_{receiver}$ or C_{donor} versus time curve.

Alternatively, the system of Equations (4.21 and 4.22) can be solved using the initial condition that, at time $t = 0$, $C_{donor} - C_{receiver} = C^{o}_{donor} - C^{o}_{receiver}$. Hence, it can be shown that:

$$K_p = \frac{V}{2At} \ln \left[\frac{C^{o}_{donor} - C^{o}_{receiver}}{C_{donor} - C_{receiver}} \right] \tag{4.22}$$

where C_{donor} and $C_{receiver}$ are the measured concentrations at time t. This approach has been used by Flynn and colleagues (e.g., Ackerman and Flynn, 1987; Behl et al., 1983a,b; Durrheim et al., 1980; Jetzer et al., 1986,1988) and many other investigators to estimate $K_{p,s}$.

Several of the recommended compound-specific $K_{p,s}$ values presented in Chapter 5 were estimated from experimentally derived J_{ss} values using this relationship and the assumption that a steady-state rate of flux exists.

The above analysis assumes that skin behaves as a homogeneous membrane with average values of diffusion coefficient, partition coefficient, and diffusion path length and in which no metabolism occurs. The measured permeability coefficient, therefore, encompasses many underlying assumptions, as well as those inherent in the use of Fick's first law. Skin is actually a very complex organ, and percutaneous absorption in vivo entails the consideration of physiological conditions often ignored in the in vitro experimental systems. The nature of the chemicals exposed to the skin and their interactions with the various tissue components determine, in large part, the appropriateness of the above assumptions. Modifications of the in vitro experimental conditions also contribute to the validity of using Fick's first law (e.g., using volatile vehicles, flow-through cells, or non-steady-state diffusion). In most cases, under steady-state diffusion, Fick's first law can be used to provide a first estimate of the permeability coefficient. To apply these values in dermal exposure assessment, one must carefully compare and evaluate the difference between the circumstances of the exposure and the well-defined conditions of the in vitro experiment used to evaluate $K_{p,s}$.

4.3.2. In Vivo Approaches

Most investigators using in vivo experimental systems reported percutaneous absorption measurements in terms of percent dose absorbed. Typically, the measurements are indirect and are based upon determination of excreted radioactivity following topical administration of the labeled chemical. The eliminated material is generally ill-defined and may be the parent compound or its metabolite(s). In most studies, the chemical is exposed to the skin at a finite dose for a defined period of time. The state of solution of crystalline permeants over the exposure period is generally uncertain. Under these experimental conditions, steady-state flux J_{ss} and $K_{p,s}$ are not easily determined from the data collected.

When a small, finite amount of a compound is applied to the skin in vivo, the compound on the surface is depleted during the time course of the study. As a result, the flux of the permeant first increases to a maximum, then decreases as the source depletes. Steady-state flux is not achieved, therefore, and determination of an unequivocal $K_{p,s}$ value is impossible. Under these conditions, the closest empirical flux value to the theoretical steady-state flux (J_{ss}) is the maximum percent dose absorbed per unit area per unit time (Guy, 1989). As a crude approximation, then, one could use the maximum rate to develop a value of $K_{p,s}$. However, this will still be an underestimate of the true $K_{p,s}$. Further drawbacks with this approach are: (a) often the manner and frequency by which data are collected are insufficient to estimate the maximum absorption rate, (b) percutaneous absorption does not always increase linearly with dose (Wester and Maibach, 1976), an outcome with several plausible explanations and dependent on the situation, and (c) it must be assumed that absorption is the slowest step in the transfer of label from the skin surface to the medium of collection (generally urine). For example, if one uses the accumulation of radioactivity in the urine as the endpoint, systemic distribution and renal elimination must be fast relative to skin permeation.

To determine $K_{p,s}$ directly from in vivo studies, pharmacokinetic data describing the absorption, distribution, metabolism, and elimination of the compound are required. A pharmacokinetic model can be constructed to include transdermal flux in the total mass balance of the compound. To simplify matters, conditions can be set so the flux approaches a quasi-steady-state condition. The body can also be represented by a physiologically based pharmacokinetic (PBPK) model. Figure 4-1 describes a PBPK model with input from all three routes of exposure: ingestion,

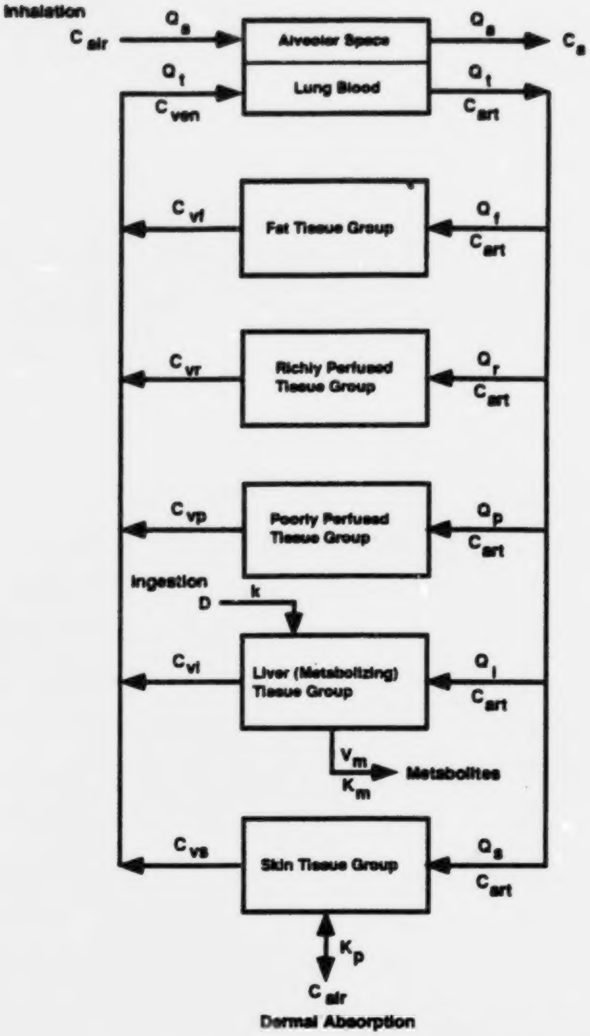
Inhalation
C air
Q a
Alveolar Space
Q a
C a
Q t
C ven
Lung Blood
Q t
C art
C vf
Fat Tissue Group
Q f
C art
C vr
Richly Perfused Tissue Group
Q r
C art
C vp
Poorly Perfused Tissue Group
Q p
C art
Ingestion
D
k
C vl
Liver (Metabolizing) Tissue Group
Q l
C art
V m
K m
Metabolites
C vs
Skin Tissue Group
Q s
C art
K p
C air
Dermal Absorption

Figure 4-1. An example of a physiologically based pharmacokinetic model.

Source: Chen and Hoang (1992)

Q_a: alveolar ventilation rate (L/min)
Q_t, Q_f, Q_r, Q_l, Q_s: blood flow rates for total cardiac output, fat, richly perfused tissue, poorly perfused tissue, liver, skin (L/min)
C_{air}, C_a, C_{ven}, C_{art}, C_{vf}, C_{vr}, C_{vp}, C_{vl}, C_{vs}: Concentrations in air, alveolar air, venous blood, arterial blood, venous blood of fat, richly perfused tissue, poorly perfused tissue, liver, skin (mg/L)
V_m: maximum velocity of metabolism (mg/min)
K_m: Michaelis Constant (mg/L)
K_p: Permeability Constant (cm/hour)
D: Gavage Dose (mg)
K: Gut Absorption time Constant (min^{-1})

inhalation, and dermal absorption (Chen and Hoang, 1992). Metabolism is depicted only in the liver. By fitting the pharmacokinetic data (concentration vs. time) to the PBPK model, a legitimate $K_{p,s}$ value can be derived. Due to the complexity of the pharmacokinetic data required for model development, these experiments can only be done in animals. Once the model is validated for one or more species of animals, appropriate physiological parameters for humans can be substituted into the model for extrapolating to human exposure. This approach has been used by Knaak et al. (1984b) for some pesticides, and by McDougal et al. (1990) to determine the permeability coefficients of several volatile organic solvents.

4.4. DEFINITIONS OF PERMEABILITY COEFFICIENTS WHEN THE MEDIUM IS NOT WATER

Although most experimental determinations of permeability coefficient have been carried out with the chemical of interest dissolved in water, exposure in the real world may involve other media, such as soil, air, neat liquids, or other nonaqueous vehicles. It is important to realize that the permeability coefficients presented in this document are vehicle-dependent, and that the permeability coefficient of benzene, for example, from an aqueous solution will be different from that of the neat liquid. It is the purpose of this section to define dermal permeability coefficients for absorption of chemicals from nonaqueous media and to relate these values to K_p^s derived for chemicals in water.

As before, we assume that the vehicle does not measurably alter the barrier properties of the skin, and we define the permeability coefficient of a chemical, which contacts the skin dissolved in an aqueous phase, as $K_{p,s}^w$, where:

$$K_{p,s}^{w} = \frac{K_{s/w} D_s}{l_s} \tag{4.23}$$

$K_{s/w}$ is the skin/water partition coefficient of the chemical, D_s is its diffusivity through the skin, and l_s is the diffusion path length across the skin.

We now define the corresponding permeability coefficients for the chemical contacting the skin from: (a) an organic (nonaqueous) solvent, (b) the pure (neat) liquid phase, (c) the vapor phase, and (d) soil.

4.4.1. Nonaqueous Solvent

As previously detailed in Section 4.2., the steady-state flux of a chemical across the skin following surface exposure to an organic solvent solution is:

$$J_{ss} = \frac{K_{s/os} \cdot D_s}{l_s} \cdot C_{os} \tag{4.24}$$

where C_{os} is the chemical concentration in the nonaqueous solvent, and $K_{s/os}$ is the skin/organic solvent partition coefficient of the chemical. It follows that the corresponding permeability coefficient $K_{p,s}^{os}$ for this exposure scenario is defined by:

$$K_{p,s}^{os} = \frac{K_{s/os} \cdot D_s}{l_s} \tag{4.25}$$

Comparison with Equation (4.2) shows that $K_{p,s}^{w}$ and $K_{p,s}^{os}$ are related by the organic solvent/water partition coefficient of the chemical ($K_{os/w}$):

$$K_{p,s}^{os} = \frac{K_{p,s}^{w}}{K_{os/w}} \tag{4.26}$$

Therefore, under ideal circumstances, if $K_{p,s}^{w}$ is known or can be reliably predicted, then $K_{p,s}^{os}$ can be estimated using the appropriate $K_{os/w}$, which can usually be approximated by $K_{o/w}$, a process much simpler than measuring a permeability coefficient.

4.4.2. Pure Liquid

The thermodynamic activity of a chemical in the neat liquid state is unity. To relate the permeability coefficient of the chemical as neat liquid ($K_{p,s}^{neat}$) to $K_{p,s}^{w}$ therefore, requires that we compare the corresponding flux equations when the chemical contacts the skin at or near unit activity from the two vehicles. In the case of aqueous solution exposure, one can do this as the solutes approach their limit of solubility in water (C_w^{sat}) and the activity approaches one. The relationship between $K_{p,s}^{neat}$ and $K_{p,s}^{w}$ is then:

$$K_{p,s}^{neat} = K_{p,s}^{w} \cdot \frac{C_w^{sat}}{\rho_{neat}} \tag{4.27}$$

where ρ_{neat} is the density of the pure liquid. Equations (4.26) and (4.27) are similar in that the ratio (ρ_{neat} / C_w^{sat}) can be considered to be an effective partition coefficient of the chemical between the neat liquid state and water, as shown in Equation (4.29).

$$K_{n/w} = \frac{\rho_{neat}}{C_w^{sat}} \tag{4.28}$$

4.4.3. Vapor Phase

By analogy with the examples above, the permeability coefficient of a chemical from the vapor phase ($K_{p,s}^{air}$) will be related to $K_{p,s}^{w}$ via an effective air/water partition coefficient ($K_{air/w}$), which may be defined as:

$$K_{air/w} = \frac{C_{air}^{sat}}{C_w^{sat}} \tag{4.29}$$

where C_v^{sat} is the concentration of chemical in the saturated vapor phase, i.e.,

$$C_{air}^{sat} = \frac{P^{sat}}{RT} \tag{4.30}$$

where, for an ideal gas, P^{sat} is the saturated vapor pressure. Thus,

$$K_{p,s}^{air} = K_{p,s}^{w} \cdot \frac{C_w^{sat} \cdot (RT)}{P^{sat}} \tag{4.31}$$

4.4.4. Soil

In the same way, the chemical's permeability coefficient from soil ($K_{p,s}^{soil}$) is related to $K_{p,s}^{w}$ by:

$$K_{p,s}^{soil} = \frac{K_{p,s}^{w}}{K_{soil/w}} \tag{4.32}$$

where $K_{soil/w}$ is the partition coefficient of the chemical between soil and water. An application of this method for estimating $K_{p,s}^{soil}$ is presented in Section 6.3.3.

4.5. THE VALUE OF THE LIMITING $K_{P,S}$ FOR CHEMICALS OF HIGH LIPOPHILICITY

It has been established experimentally (e.g., Durrheim et al., 1980) that skin stripped of its stratum corneum is not infinitely permeable; rather, it retains a residual resistance due to the diffusional barrier of the underlying viable tissue. The residual permeability of hairless mouse skin, stripped of its stratum corneum, is on the order of 0.1 cm/hour. In man, the thickness of the viable epidermis (l_{ve}) between the inner surface of the stratum corneum and the upper dermal capillary plexus is on the order of 100 μm. The diffusive medium for a molecule in the viable epidermis is essentially aqueous, and typical diffusion coefficients for nonelectrolytes of moderate size in light liquids are expected to be in the range of 10^{-6} cm^2/second to 10^{-5} cm^2/second (Cussler, 1984). However, the diffusion coefficient through the viable epidermis (D_{ve}) is expected to be somewhat smaller (by roughly a factor of 1/5 to 1/3 [Scheuplein, 1965]). Assuming that the partition coefficient between the viable epidermis (which is essentially an aqueous medium) and water to be about one, the permeability coefficient of the chemical through this sub-stratum corneum resistance is given by:

$$K_{p,ve}^{\lim} = \frac{D_{ve}}{l_{ve}} \tag{4.33}$$

where the subscript, ve, stands for viable epidermis. Substituting a value of D_{ve} in the range of 0.26 x 10^{-6} cm^2/second to 0.33 x 10^{-5} cm^2/second, and a value for l_{ve} of 100 μm, we calculate that:

$$K_{p,ve}^{\lim} \approx 0.1 - 1.0 \ cm/hr \tag{4.34}$$

An alternative interpretation for the limiting permeability of the skin is that, for compounds of very high lipophilicity, the transport out of the stratum corneum (rather than transport through the stratum corneum) is the rate-determining step in the overall penetration process (Guy and Hadgraft, 1988). Therefore, the significant physical event is the interfacial transfer of the chemical from the lipophilic stratum corneum into the aqueous underlying viable tissue. While such heterogeneous rate constants have not been measured in the skin, they have been determined at model membrane-water interfaces. Typical values (Guy et al., 1984) are on the order of 10^{-4} cm/sec or about 0.36 cm/hour, which is about the mid-point of the values of $K_{p,ve}^{\lim}$ estimated above. Therefore, it seems reasonable to expect that experimentally measured permeability coefficients for chemical penetration across the skin from aqueous media (assuming that the chemical does not alter the barrier properties) are limited to 1 cm/hour.

4.6. ESTIMATION OF ABSORBED DOSE

The above discussion describes the theoretical basis of the measurement of the permeability coefficient $K_{p,s}$ from experimental studies under steady-state conditions. In actual exposure scenarios, time is required after initial contact with the skin for such a steady-state to be achieved. This unsteady-state period is a function of the lag time (τ) as defined in Section 4.1., and it is depicted in Figure 4-2.

For the purpose of risk assessment, the total amount of chemical that becomes systemically available over all time as a result of exposure should be used. Indications are that this value is better approximated by the amount of material which has entered the skin than by the amount which has traversed the skin and entered the blood during the exposure period. During the non steady-state period, the amount of chemical entering the skin is greater than that exiting the skin. Steady-state occurs when the concentration gradient across the entire barrier layer is constant, and the rate that the chemical enters the skin equals the rate that it exits. Therefore, an appropriately conservative estimate of the total exposure should be calculated based upon the amount crossing the exposed (outside) skin surface and not the amount that fluxes out of the skin and into the body during the exposure time. Any chemical absorbed into the stratum corneum will continue to flux into the viable tissue layers. If there is no loss of the chemical present in the skin by metabolism, irreversible binding, evaporation, or desquamation, etc., then all of the chemical, which entered the skin during the exposure period, will eventually become available to the body.

To emphasize the difference between the amounts of chemical entering and leaving the stratum corneum during the exposure period, Figure 4-3 shows the cumulative mass of chemical entering the stratum corneum through the exposed (outside) surface as a function of time, as well as the mass of chemical leaving the inside surface. Fick's first law is depicted by the straight line through the origin. The linear regions (i.e., where cumulative amount increases proportionally with time) correspond to steady-state conditions and have identical slopes. The regions prior to steady-state are clearly different, i.e., the total mass entering the skin is always larger than the total mass exiting the skin. To get a conservative estimate of the total mass absorbed, the upper curve should always be used.

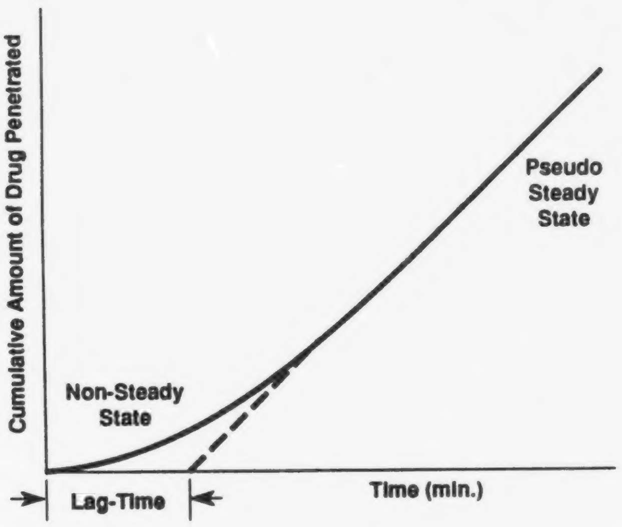

Figure 4-2. Cumulative amount of chemical fluxing out of the stratum corneum as a function of time. Lag time is indicated.

Source: Hadgraft (1983)

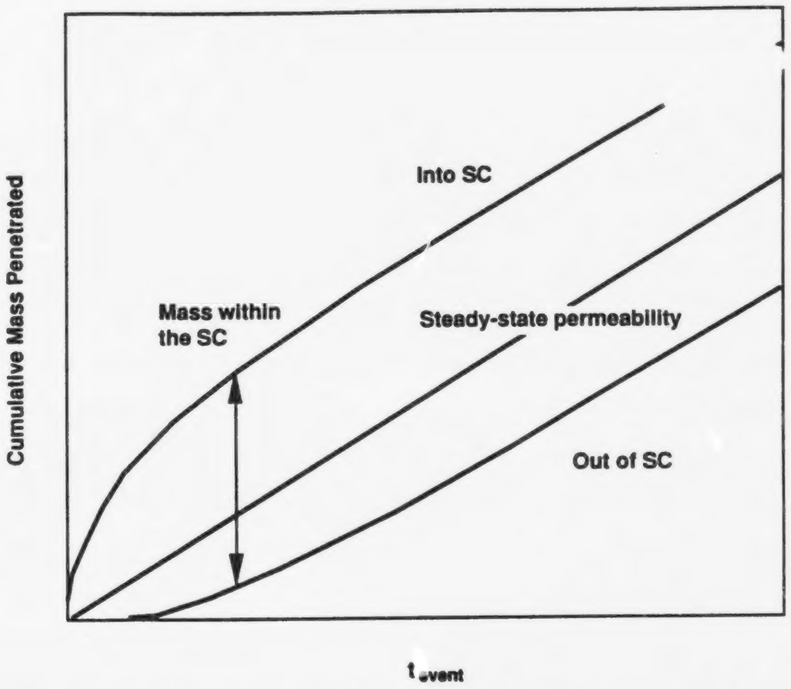

Figure 4-3. Cumulative amount of chemical entering the stratum corneum through the exposed (outside) surface and exiting the inside surface as a function of time.

Source: Cleek and Bunge, 1992

For highly lipophilic compounds, the viable epidermis also serves as a significant resistance to penetration into the skin. The time for these compounds to reach steady-state may be on the order of hours (Dugard, 1986), and therefore can have a significant impact on the use of the simple steady-state Fick's first law (Equation 4.1) in the evaluation of the dermally absorbed dose for chemical exposure in environmentally relevant scenarios. The resulting flux through the skin becomes a function of both the exposure period and the physico-chemical properties of the chemicals as they influence the relative resistance of these two layers. This effect of the viable epidermis on the cumulative mass which enters the stratum corneum can be characterized by a parameter B, which describes the relative contribution of the permeability coefficients of the chemical in the stratum corneum and the viable epidermis. This parameter B is defined as (Cleek and Bunge, 1992):

$$B = K_{ve/v} \frac{K_{p,sc}\ K_{sc/ve}}{K_{p,ve}\ K_{sc/v}} \tag{4.35}$$

where $K_{p,sc}$ and $K_{p,ve}$ are the permeability coefficients of the chemical in the stratum corneum and the viable epidermis respectively, $K_{sc/v}$ and $K_{ve/v}$ are the partition coefficients of the chemical between the respective two layers and the vehicle, and $K_{sc/ve}$ is the equilibrium partition coefficient between the stratum corneum and the viable epidermis. The epidermis is often viewed as a hydrous mass and consequently $K_{sc/ve}$ correlates directly with the octanol-water partition coefficient, $K_{o/w}$. Consequently, increasing chemical lipophilicity causes B to become larger. As an initial estimate based on literature values of the magnitude of these variables, B can be approximated by the following equation (Cleek and Bunge, 1992):

$$B \approx \frac{K_{o/w}}{10{,}000} \tag{4.36}$$

To compare chemicals with different partition coefficients and effective diffusion coefficients, Figure 4-4 shows the cumulative mass absorbed into the stratum corneum per unit area normalized by the quantity ($K_{sc/v}\ C_v^o\ l_{sc}$) as a function of the dimensionless time (t/τ). Figure 4-4 illustrates several important features of how chemicals are absorbed into the stratum corneum which should be

For highly lipophilic compounds, the viable epidermis also serves as a significant resistance to penetration into the skin. The time for these compounds to reach steady-state may be on the order of hours (Dugard, 1986), and therefore can have a significant impact on the use of the simple steady-state Fick's first law (Equation 4.1) in the evaluation of the dermally absorbed dose for chemical exposure in environmentally relevant scenarios. The resulting flux through the skin becomes a function of both the exposure period and the physico-chemical properties of the chemicals as they influence the relative resistance of these two layers. This effect of the viable epidermis on the cumulative mass which enters the stratum corneum can be characterized by a parameter B, which describes the relative contribution of the permeability coefficients of the chemical in the stratum corneum and the viable epidermis. This parameter B is defined as (Cleek and Bunge, 1992):

$$B = K_{ve/v} \frac{K_{p,sc}\ K_{sc/ve}}{K_{p,ve}\ K_{sc/v}} \qquad (4.35)$$

where $K_{p,sc}$ and $K_{p,ve}$ are the permeability coefficients of the chemical in the stratum corneum and the viable epidermis respectively, $K_{sc/v}$ and $K_{ve/v}$ are the partition coefficients of the chemical between the respective two layers and the vehicle, and $K_{sc/ve}$ is the equilibrium partition coefficient between the stratum corneum and the viable epidermis. The epidermis is often viewed as a hydrous mass and consequently $K_{sc/ve}$ correlates directly with the octanol-water partition coefficient, $K_{o/w}$. Consequently, increasing chemical lipophilicity causes B to become larger. As an initial estimate based on literature values of the magnitude of these variables, B can be approximated by the following equation (Cleek and Bunge, 1992):

$$B \approx \frac{K_{o/w}}{10{,}000} \qquad (4.36)$$

To compare chemicals with different partition coefficients and effective diffusion coefficients, Figure 4-4 shows the cumulative mass absorbed into the stratum corneum per unit area normalized by the quantity ($K_{sc/v}\ C_v^o\ l_{sc}$) as a function of the dimensionless time (t/τ). Figure 4-4 illustrates several important features of how chemicals are absorbed into the stratum corneum which should be considered in estimating the amount of chemical absorbed during an exposure event. First, the normalized mass of chemical absorbed per unit area $[DA_{event}/(A\ K_{sc/v}\ C_v^o\ l_{sc})]$ during exposure times shorter than the time required to reach steady-state is independent of B. After the initial unsteady-state period, the presence of the viable epidermis is felt, and the normalized cumulative mass absorbed depends on B as illustrated in Figure 4-4. For moderately lipophilic or hydrophilic compounds (log $K_{o/w}$ approximately less than 1), B will be less than 0.1 and the cumulative mass of chemical which is absorbed will continue to be controlled solely by the stratum corneum. As compounds increase in lipophilicity, the viable epidermis will restrict the flux of chemicals leaving the stratum corneum. If $K_{o/w}$ is large enough ($B > 100$ or log $K_{o/w}$ of approximately 5), the viable epidermis entirely controls the steady-state flux of the chemical.

Given the permeability coefficient $K_{p,s}$ of any chemical, the total mass per unit area (M/A) entering through the exposed surface during the exposure period, as expressed by Fick's first law at steady-state can be evaluated as follows:

$$DA_{event} = \frac{M}{A} = K_{p,s}\ C_v\ t_{event} \tag{4.37}$$

This equation has been used traditionally to estimate the absorbed dose from dermal exposure to environmental contaminants. Assuming that $K_{p,s}$ represents the steady-state flux through the skin (including both the stratum corneum and the viable epidermis), the straight line passing through the origin in Figure 4-3 depicts the accumulated amount of chemical absorbed as evaluated by Equation (4.37). Therefore, the total amount absorbed in actual exposure scenarios would always be underestimated using this equation. Cleek and Bunge (1992) have developed the following general scheme to estimate (M/A) in actual exposure scenarios, depending on whether the exposure period is shorter or longer than the unsteady-state period of the flux of chemicals through the skin.

When the exposure time is shorter than the unsteady-state period, the absorbing chemical has not reached the interface between the stratum corneum and viable epidermis, and consequently the additional barrier of the viable epidermis is not felt yet. As shown in Figure 4-4, the total amount of

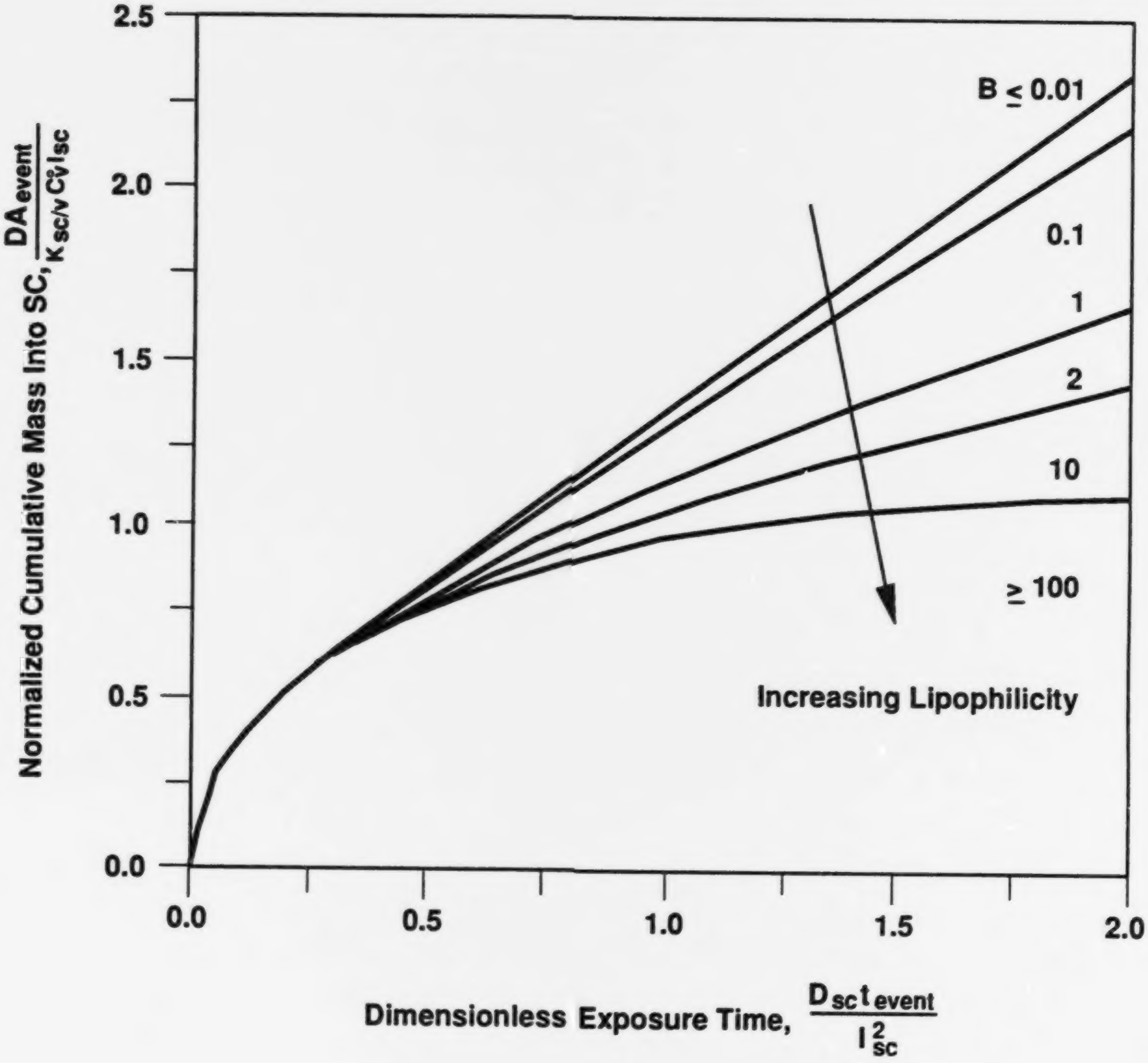

Figure 4-4. Cumulative mass entering the stratum corneum including the viable epidermis.
Source: Cleek and Bunge, 1992

chemical absorbed during this period is independent of B. It has been shown by Cleek and Bunge (1992) that this initial unsteady-state period can accurately be depicted by modeling the diffusion through the stratum corneum as if it is a semi-infinite membrane (a discussion of this classical transport problem of diffusion through a semi-infinite slab can be found in most textbooks on transport phenomena, e.g., Cussler, 1984). Consequently, the mass absorbed per unit area during the unsteady-state time period can be estimated with the following simple expression:

$$DA_{event} = \frac{M}{A} = 2\ K_{p,sc}\ C_v \sqrt{\frac{6\ \tau\ t_{event}}{\pi}} \tag{4.38}$$

When the exposure time exceeds the unsteady-state period, Cleek and Bunge (1992) have shown that the cumulative mass absorbed into the skin can be estimated by assuming that the skin is composed of two adjacent layers, the stratum corneum and the viable epidermis. Cleek and Bunge (1992) derived an analytical solution to this transport problem of chemical diffusion through a slab composed of two layers of finite thickness. The total mass absorbed per unit area in both layers after the exposure duration can be estimated by the following equation:

$$DA_{event} = \frac{M}{A} = K_{p,sc}\ C_v \left[\frac{t_{event} + 2\left(1 + 3B\right)\tau}{1 + B}\right] \tag{4.39}$$

Whether to use Equation (4.38) or Equation (4.39) depends on the duration of the exposure and the value of B. Based on calculations by Cleek and Bunge (1992), the time it takes to reach steady-state (t^*) can be evaluated as a function of B:

For B $\leq$ 0.1

$$t^* = 2.4\ \tau \tag{4.40}$$

For 0.1 $\leq$ B $\leq$ 1.17

$$t^* = \left(8.4 + 6 \log B\right) \tau \tag{4.41}$$

For B $\geq$ 1.17, t^* is given by:

$$t^* = 6 \left(b - \sqrt{b^2 - c^2}\right) \tau \tag{4.42}$$

where b and c are defined as:

$$b = \frac{2}{\pi} \left(1 + B\right)^2 - c \tag{4.43}$$

$$c = \frac{1 + 3B}{3} \tag{4.44}$$

Equations (4.38) through (4.44) require estimates of τ, $K_{sc/v}$ and l_{sc}. Given a value of the permeability coefficient $K^{w}_{p,s}$ and assuming that the stratum corneum provides the main resistance to diffusion, τ can be approximated by:

$$\tau = \frac{l_{sc}^2}{6\ D_{sc}} \tag{4.45}$$

$$\log \frac{D_{sc}}{l_{sc}} = \log K^{w}_{p,sc} - \log K_{sc/w} \tag{4.46}$$

$$l_{sc} \approx 10 - 20\ \mu m \tag{4.47}$$

$$\log K_{sc/w} = 0.7 \log K_{o/w} \tag{4.48}$$

Equation (4.48) assumes that the chemical is being absorbed into the skin from an aqueous vehicle. Adjustments for absorption from other vehicles can be obtained simply by substituting the appropriate correlations among the permeability coefficients as discussed in previous sections.

5. DERMAL ABSORPTION OF COMPOUNDS FROM WATER

This chapter focuses on the dermal absorption of compounds in water. First, the experimental data on permeability coefficients (K_p) for aqueous media are reviewed and recommendations are made for approximately 70 compounds. Second, procedures for predicting aqueous permeability coefficients are reviewed, and recommendations are made for estimating K_p. Finally, procedures for evaluating the dermal dose absorbed using the approach developed in Chapter 4 are presented with the assumptions to estimate the required parameters.

5.1. EXPERIMENTALLY DERIVED K_P VALUES

This section discusses experimental data on K_p values for environmental contaminants in water. A strategy for reviewing and evaluating the data is presented, and then, the results of this review and recommended K_p values are summarized.

5.1.1. Strategy for Reviewing Experimental Data

The following strategy was used to evaluate and assess the uncertainty of experimentally derived permeability coefficients (K_p). The strategy was derived from Chapters 2 and 3 conclusions and involves four levels: minimal requirements, first-order factors, second-order factors, and statistical factors, as described below.

1. Minimal Requirements: In order for experimental data to be considered, the following requirements must be met:

    - Skin Condition - Numerous studies have shown that diseased or injured skin is generally more permeable to chemical compounds than healthy, intact skin (see Chapter 2). Thus, only experiments using undamaged skin were considered. Clipping hair from the skin of experimental animals may be necessary to improve contact with the skin and avoid leaks in diffusion chambers. However, if not done carefully, this process may also damage the skin and result in artificially high estimates of K_p. Ideally, testing should not begin until 24 hours after clipping to allow time for any necessary healing to occur.

- Vehicle - Permeation is a vehicle dependent process and vehicles other than water, (i.e, oils, soil, etc.) are associated with permeability rates substantially different than those involving water. Neat lipophilic compounds often have higher penetration rates but lower K_p estimates than compounds dissolved in water. For example, Blank and McAuliffe (1985) report that the flux for neat benzene is 1.2 $\mu L/cm^2$ and for benzene dissolved in water is 0.22 $\mu L/cm^2$. Further, they report that the K_p for neat benzene is 0.002 cm/hour and K_p for benzene dissolved in water is 0.2 cm/hour. Since water is the medium of concern, only K_p data derived from studies using water as a vehicle were considered.

- Published Data - Only published and peer-reviewed data were considered.

2. First-Order Factors: These factors represent experimental conditions or approaches that have the strongest influence on how well the K_p estimates represent the actual permeability occurring in human exposure to contaminants in water. They are the primary basis for evaluating experimental data and assessing their uncertainty.

    - In Vivo vs. In Vitro - Theoretically, human in vivo data should provide the most realistic estimates of K_p applicable to human exposure. However, human testing is usually not an option or is difficult to conduct under controlled conditions. Chapters 2 and 3 recommend measuring aqueous permeability coefficients using both in vivo and in vitro techniques. This usually means that human in vitro testing is done and results are compared to in vivo animal data. The rationale for this approach is that the in vitro experiments allow the use of human skin and are more easily implemented than in vivo experiments. However, they may not accurately mimic the processes in living systems such as blood flow, metabolism, and other pharmacokinetic processes. Thus ideally, the in vitro experiments should be used as the primary means of studying dermal absorption, but substantiated to the degree possible with in vivo experiments. Where results of in vivo and in vitro experiments on the same contaminant differ significantly, judgement should be used to decide which is the more reliable, and the selected value must be identified as much more uncertain than values supported by both approaches.

    - In Vitro Method - In vitro experiments using continuous flow and infinite dose procedures are the most reliable for assessing permeability coefficients. Continuous flow systems mimic the capacity of the circulatory system to remove penetrants and maintain a negligible contaminant concentration under the skin. Infinite dose procedures, along with continuous flow collection ensure that steady-state conditions are obtained.

    - In Vivo Method - In vivo experiments should be done to allow periodic collection of data indicating that steady-state conditions have been established. It is important that the permeant be applied in a vehicle and in such a manner that its thermodynamic driving force (concentration) remains constant or nearly so. Data obtained under conditions where the physical state of permeant on skin is unknown are at best qualitative.

- Data Analysis Method - Estimation of K_p from in vitro experiments is relatively straight forward since steady-state conditions are fairly easily maintained, accumulation of the penetrant in the receiving fluid can be directly measured and many of the complicated pharmacokinetic processes of a living system are not involved. However, these conditions do not apply as well to tests conducted in vivo. The accumulation of the penetrant in the body is more difficult to measure since it can be transported to many different fluids and tissues and metabolized or eliminated. In small rodent studies it may be feasible to conduct a whole body bioassay to measure the total absorbed dose. Since measurement of permeant accumulation in all body compartments is usually not practical to measure, some researchers have instead measured the disappearance of the permeant from the material applied to the skin surface. Almost all of the currently available human in vivo data for environmental contaminants were obtained this way. This procedure provides only indirect evidence that penetration has occurred and involves several uncertainties: contaminant loss may occur by processes other than skin permeation such as volatilization, the small reductions in concentration (of permeant in applied solution) over the course of the experiment can be difficult to measure accurately and estimation of the exposed skin area may be difficult. Alternative approaches involve measuring permeant levels in tissue, blood, breath, or excreta. However, since these levels do not represent the entire body burden, further adjustment of the dose estimate is required. Feldman and Maibach (1967) introduced a procedure comparing contaminant levels in urine from equal doses applied dermally and intravenously. The assumption is made that the fraction of the intravenous dose reaching the urine can be used to adjust the urine levels resulting from a dermal dose to get the total absorbed dose. Although this approach appears to be a significant improvement over the disappearance approach, it still may not accurately account for all pharmacokinetic processes. Ideally, in vivo data should be interpreted using physiologically based pharmacokinetic (PBPK) models which account for metabolism, blood flow, elimination, and other systemic processes that can affect dermal absorption. However, PBPK models and the input data they require are not readily available for most chemicals.

- Species - Numerous studies have shown animal skin to be more permeable to environmental pollutants and other compounds than human skin (see Chapters 2 and 3). Studies have shown that mouse, rabbit, rat, and guinea pig skin generally tends to overpredict human K_p values significantly, and that monkey and swine skin generally provide permeation rates more comparable to those found for humans. Whenever possible, K_p values from studies in which human skin is used were given the greatest priority.

- Metabolism - Metabolism of compounds in the skin can reduce the amount of parent compound absorbed into the body. At the same time, metabolites have different properties than the parent in terms of permeability and toxicity. In vitro tests conducted using nonviable skin overestimate the extent of dermal absorption of intact compound in situations where skin metabolism occurs. In vivo tests can also misrepresent metabolism effects in situations where radioactive labels are used, since distinctions between the intact permeant and its metabolites are generally not made. Uncertainty about metabolic effects is also introduced in animal studies using either in vitro or in vivo methods since animal skin can have different metabolic capacities than human skin. Thus, metabolism is an important and difficult factor to place into perspective. Generally, tests using viable human skin should provide the best representation of human metabolic processes. Viable skin is defined for this purpose as skin that maintains the metabolic capacity of the living system. Metabolic capacity can be evaluated by measuring oxygen consumption and glucose utilization. Experimental procedures that help ensure viability involve the use of unaltered skin soon after removal from a living system. Chemical treatment such as embalming or storage procedures such as freezing are likely to eliminate or reduce viability. Special procedures such as the application of tissue nutrients may be needed to maintain viability over the duration of the experiment.

The first-order factors were used to derive a scoring system designed to provide a preliminary indication of how well the K_p estimates should represent the actual permeability occurring during human exposure to water contaminants. As shown in Table 5-1, a score is selected for each criterion, summed, and then multiplied by 5 to yield a 100-point scale. Higher scores correspond to more reliable K_p estimates for use in human exposure assessments.

All approaches to estimating K_p's involve uncertainties. Insufficient information is available to accurately assess the level of uncertainty, but they probably could vary about plus or minus a half order of magnitude from the best estimate values. Generally, estimates with a high weight-of-evidence score should be less uncertain than those with lower scores. Relative to the other parameters in exposure assessment K_p's are probably one of the more uncertain, although this is difficult to demonstrate quantitatively. Qualitatively, the general sources of uncertainty associated with the various approaches are described below:

- Experimental Error - All approaches potentially involve error in measuring permeant levels in various media and maintaining experimental conditions to ensure achievement of steady-state. This error is probably greater in the in vivo experiments since conditions are harder to control.

- Conceptual Uncertainty in Procedures and Data Analysis - Derivation of K_p's from in vitro data using Fick's first law is reasonably valid because the underlying assumptions can be maintained. However, this is less true for in vivo data. As discussed previously, the various procedures used to estimate K_p from in vivo data involve varying degrees of uncertainty. The disappearance method is highly uncertain, and bioassay data adjusted to get total dose (where needed) is less uncertain.

- Uncertainty in Extrapolation: Animal vs. Human - All animal skin experiments introduce additional uncertainty over human skin experiments because animal skin can differ from human skin in many ways and thus may not accurately represent the permeation characteristics of human skin. Ideally PBPK models would be used to extrapolate animal data to humans, but such models are not currently readily available. Thus, the procedure taken in this document is to use K_p's estimated from animal data (when human data are not available) and assume they apply directly to humans. Assessors should understand that this assumption introduces additional uncertainty.

In vivo vs in vitro - In vitro data may not accurately mimic the processes of a living system. For example, metabolic processes may be reduced or eliminated during in vitro experiments. Thus, in vitro experiments introduce additional uncertainty over in vivo experiments in this regard.

Table 5-1. Weight-of-Evidence Scoring System

In Vitro:		
Species:	Human	10
	Monkey, Pig	6
	Rat, Guinea Pig	4
	Mouse, Rabbit	2
Continuous Flow:	Yes	2
	No	0
Infinite Dose:	Yes	4
	No	0
Metabolic Capacity Maintained:	Yes	4
	No	0
	Sum:	x 5=
In Vivo:		
Species:	Human	10
	Monkey, Pig	6
	Rat, Guinea Pig	4
	Mouse, Rabbit	2
Procedure:	Body Burden Measurement	4
	Disappearance Method	1
PBPK Model Used to Derive K_p:	Yes	3
	No	0
Steady-state Demonstrated:	Yes	3
	No	0
	Sum:	x 5=

3. Second Order Factors - These factors are experimental conditions known to influence K_p estimates, but have less impact on how representative the estimates are of human contact with water than the first-order factors. The influence of these factors on the magnitude of the K_p estimate can be appreciable. They can be used qualitatively or for purposes of selecting one experimental result over another.

- Gender - As shown in Chapter 2, skin from some female animals has been shown to be more permeable to applied compounds than skin from male animals. Therefore, to allow a more conservative estimate of absorbed dose to be made, K_p values generated from studies using female skin were selected over those using male skin, if all other parameters were equal.

- Age - A trend toward increased permeability of the skin has been shown in studies using premature infants and slightly decreased permeability has been demonstrated in young and aged animals (see Chapter 2). Although K_p values for individuals in these age categories would be the most conservative, they would not be representative of the majority of the population. Therefore, studies in which these age groups were used received less priority for selection than dermal absorption studies of animals or humans in the middle-age range, if all other parameters were equal.

- Location - As discussed in Chapter 2, skin permeability varies with location on the body due to differences in quality and thickness of the stratum corneum. Lipid content, structure, and other factors may also account for differences. Most parts of the body (abdomen, forearm, forehead, back) have a stratum corneum thickness of 10 - 16 μm. Human skin from these areas would be more representative of whole body exposure during bathing or swimming than areas with much thicker skin (i.e., palm, sole) or thinner skin (i.e., scrotum). Animal skin from locations with comparable thickness to human torso skin would be preferable over locations with different thicknesses.

- Chemical Concentration - Since K_p is defined as flux normalized for concentration, K_p values should remain constant over a range of concentration values. However, situations involving high concentrations of organic solvents can extract lipids from the stratum corneum, thereby altering the diffusional barrier properties of this layer. Since such high concentrations can cause K_p to change and since most environmental contaminants occur at low concentrations, studies using relatively dilute solutions of the compound of interest were selected over those that used more concentrated solutions.

- Occlusion/Hydration - Occlusion of the site of application on the skin (e.g., with plastic wrap in vivo, or by covering the diffusion chamber in vitro) results in hydration of the stratum corneum and subsequent increased permeability of this layer relative to a nonoccluded state (see Chapter 3). Since this increased degree of hydration after occlusion corresponds to the degree of hydration most likely found during bathing, showering, or wading, studies using occluded conditions were selected over studies using a nonoccluded skin site, if all other factors were equal.

- Temperature - In vitro studies have shown that raising the donor solution temperature above 37°C, such as might occur in a bathing or showering scenario, increases K_p, while lowering the donor temperature below 37°C, such as might occur during swimming scenarios, reduces K_p (see Chapter 3). As a result, attempts were made to select a K_p for each compound that was obtained in a study in which the temperature of the donor solution approximated that of the aqueous environment for each scenario (around 40°C for bathing/showering and about 20°C for swimming). Unfortunately many studies do not report this information.

- Duration - K_p should be estimated under steady-state conditions, so longer duration experiments are preferable to shorter duration (where infinite dose is used, not if finite dose is used).

- pH - Human contact with water during bathing and swimming generally involves pH conditions near neutral. So experimental conditions near a neutral pH are preferable over nonneutral conditions.

4. Statistical Factors - These factors represent experimental procedures affecting data quality rather than physical conditions of the experiments.

   - Number of Animals - A study using a greater number of animals/treatment group was given a higher priority over one with fewer animals for reasons of statistical significance.

   - Number of Replicates - Studies that used more replicates/dose were selected over those that used fewer replicates/dose because of the increased scientific validity and statistical significance of these results, assuming all other factors are equal.

The second order and statistical factors are summarized in Table 5-2.

Table 5-2. Second Order and Statistical Criteria for Reviewing K_p Data

Parameter	Higher Priority	Lower Priority
Gender	Female[a]	Male
Age	Middle range[b]	Young or aged
Location	Torso[b]	palms, soles, scrotum
Chemical Concentrations	Lower[b]	Higher
Occluded/Hydrated	Yes[b]	No
Temperature	Similar to scenario	Different
Duration	Longer[c]	Shorter
pH	Neutral[b]	Not Neutral
Number of animals	More[d]	Less
Number of replicates	More[d]	Less

[a] Results in more conservative estimate of dose (animals).
[b] Corresponds more closely to exposure scenario.
[c] Infinite dose not finite dose.
[d] More scientifically/statistically valid results.

5.1.2. Recommended K_p Values

Using the above strategy the current literature was reviewed, and K_p values for about 70 compounds of potential environmental interest were evaluated. The recommended values for each of these compounds are summarized in Table 5-3. The supporting evidence for each compound is summarized in the Appendix to this Chapter. These summaries also describe the basis for developing the weight-of-evidence score.

Table 5-3. Experimentally Measured Permeability Coefficient Values for Compounds in Aqueous Media

Chemical	K_p (cm/hr)	Skin Type	Method	Weight of Evidence	Reference
2-Amino-4-nitrophenol	7x 10^{-4}	Human	Vitro	70	Bronaugh and Congdon, 1984
4-Amino-2-nitrophenol	3x 10^{-3}	Human	Vitro	70	Bronaugh and Congdon, 1984
Aniline	4x 10^{-2}	Human	Vivo	55	Baranowska-Dutkiewicz, 1982
Benzene	1x 10^{-1}	Human	Vitro	70	Blank & McAuliffe, 1985
p-Bromophenol	4x 10^{-2}	Human	Vitro	70	Roberts et al., 1977
2,3-Butanediol	<5x 10^{-5}	Human	Vitro	70	Blank et al., 1967
Butanol	2x 10^{-3}	Human	Vitro	50	Scheuplein and Blank, 1973
2-Butanone	5x 10^{-3}	Human	Vitro	70	Blank et al., 1967
2-Butoxyethanol	1x 10^{-2}	G.Pig	Vivo	55	Johanson and Fernstrom, 1988
Cadmium Compounds					
Cadmium chloride	1x 10^{-3}	G.Pig	Vivo	25	Skog and Wahlberg, 1964
Carbon disulfide	5x 10^{-1}	Human	Vivo	55	Baranowska-Dutkiewicz, 1982
Chlorocresol	5x 10^{-2}	Human	Vitro	70	Roberts et al., 1977
Chloroform	1x 10^{-1}	G.Pig	Vivo	55	Bogen et al., 1992
2-Chlorophenol	3x 10^{-2}	Human	Vitro	70	Roberts et al., 1977
p-Chlorophenol	4x 10^{-2}	Human	Vitro	70	Roberts et al., 1977
Chloroxylenol	6x 10^{-2}	Human	Vitro	70	Roberts et al., 1977
Chromium Compounds					
Sodium chromate	2x 10^{-3}	Human	Vivo	55	Baranowska-Dutkiewicz, 1981
Sodium dichromate	1x 10^{-3}	G.Pig	Vivo	25	Wahlberg, 1968
Chromium chloride	1x 10^{-3}	G.Pig	Vivo	25	Wahlberg and Skog, 1965
Cobalt Compounds					
Cobalt chloride	4x 10^{-4}	Human	Vitro	70	Wahlberg, 1965b
m-Cresol	1x 10^{-2}	Human	Vitro	70	Roberts et al., 1977
o-Cresol	2x 10^{-2}	Human	Vitro	70	Roberts et al., 1977
p-Cresol	2x 10^{-2}	Human	Vitro	70	Roberts et al., 1977
Decanol	8x 10^{-2}	Human	Vitro	70	Scheuplein and Blank 1973
2,4-Dichlorophenol	6x 10^{-2}	Human	Vitro	70	Roberts et al., 1977
2,4-Dimethylphenol	1x 10^{-1}	Mouse	Vitro	45	Huq et al., 1986
2,4-Dinitrophenol	<3x 10^{-3}	Mouse	Vitro	45	Huq et al., 1986
1,4-Dioxane	4x 10^{-4}	Human	Vitro	70	Bronaugh, 1982
Ethanol	8x 10^{-4}	Human	Vitro	50	Scheuplein and Blank, 1973
2-Ethoxyethanol	3x 10^{-4}	Human	Vitro	70	Blank et al., 1967
Ethylbenzene	1	Human	Vivo	55	Dutkiewicz and Tyras, 1967
Ethyl ether	2x 10^{-2}	Human	Vitro	70	Blank et al., 1967
p-Ethylphenol	3x 10^{-2}	Human	Vitro	70	Roberts et al., 1977
Glucose	9x 10^{-5}	Mouse	Vitro	50	Ackermann and Flynn, 1987
Glycerol	1x 10^{-4}	Mouse	Vitro	50	Ackermann and Flynn, 1987
Heptanol	4x 10^{-2}	Human	Vitro	70	Blank et al., 1967
Hexanol	3x 10^{-2}	Human	Vitro	80	Bond and Barry, 1988

Table 5-3. (continued)

Chemical	K_p (cm/hr)	Skin Type	Method	Weight of Evidence	Reference
Lead Compounds					
Lead acetate	4x 10^{-6}	Human	Vivo	70	Moore et al., 1980
Mercury Compounds					
Mercuric chloride	1x 10^{-3}	Human	Vitro	80	Wahlberg, 1965a
Methyl mercury-dicyandiamide	1x 10^{-3}	G.Pig	Vivo	25	Friberg et al., 1961
Pottassium mercuric-chloride	3x 10^{-3}	G.Pig	Vivo	55	Wahlberg and Skog, 1962
Methanol	2x 10^{-3}	Human	Vitro	70	Southwell et al., 1984
Methyl ethyl ketone	5x 10^{-3}	Human	Vitro	70	Blank et al., 1967
Methyl hydroxybenzoate	9x 10^{-3}	Human	Vitro	70	Roberts et al., 1977
ß-Naphthol	3x 10^{-2}	Human	Vitro	70	Roberts et al., 1977
Nickel Compounds					
Nickel chloride	1x 10^{-4}	Human	Vitro	70	Fullerton et al., 1988
Nickel sulfate	9x 10^{-6}	Human	Vitro	70	Samitz and Katz, 1976
2-Nitrophenol	1x 10^{-1}	Mouse	Vitro	45	Huq et al., 1986
3-Nitrophenol	6x 10^{-3}	Human	Vitro	70	Roberts et al., 1977
4-Nitrophenol	6x 10^{-3}	Human	Vitro	70	Roberts et al., 1977
n-Nitrosodiethanolamine	5x 10^{-6}	Human	Vitro	70	Bronaugh et al., 1981
Nonanol	6x 10^{-2}	Human	Vitro	70	Scheuplein and Blank, 1973
Octanol	6x 10^{-2}	Human	Vitro	70	Southwell et al., 1984
Pentanol	6x 10^{-3}	Human	Vitro	70	Scheuplein and Blank, 1973
Phenol	8x 10^{-3}	Human	Vitro	70	Roberts et al., 1977
Propanol	2x 10^{-3}	Human	Vitro	70	Blank et al., 1967
Resorcinol	2x 10^{-4}	Human	Vitro	70	Roberts et al., 1977
Silver Compounds					
Silver nitrate	6x 10^{-4}	Human	Vivo	55	Norgaard, 1954
Styrene	7x 10^{-1}	Human	Vivo	55	Dutkiewicz and Tyras, 1968
Tetrachloroethylene	4x 10^{-1}	G.Pig	Vivo	55	Bogen et al., 1992
Thiourea	1x 10^{-4}	Mouse	Vitro	50	Ackermann and Flynn, 1987
Thymol	5x 10^{-2}	Human	Vitro	70	Roberts et al., 1977
Toluene	1	Human	Vivo	55	Dutkiewicz and Tyras, 1968
Trichloroethylene	2x 10^{-1}	G.Pig	Vivo	55	Bogen et al., 1992
2,4,6-Trichlorophenol	6x 10^{-2}	Human	Vitro	70	Roberts et al., 1977
Urea	1x 10^{-4}	Mouse	Vitro	50	Ackermann and Flynn, 1987
Water	1x 10^{-3}	Human	Vitro	80	Bronaugh et al., 1986b
3,4-Xylenol	4x 10^{-2}	Human	Vitro	70	Roberts et al., 1977
Zinc Compounds					
Zinc chloride	6x 10^{-4}	G. Pig	Vivo	25	Skog and Wahlberg, 1964

5.2. METHODS FOR PREDICTING PERMEABILITY COEFFICIENT OF AQUEOUS CONTAMINANTS

From the current literature, two general types of structure-activity models, empirical and theoretical, have been proposed to estimate skin permeability coefficients of chemicals from aqueous solutions:

- Empirical models are based on actual experimental permeability coefficients of structurally related chemicals. In general, the permeability coefficients of a series of congeneric compounds are measured, and then permeability is correlated with some physico-chemical property(ies), such as partition coefficient and molecular weight. The derived relationships are then employed to predict the permeability coefficients of other structurally similar compounds. Using several key physico-chemical descriptors together and simultaneously, this type of approach can be extended to cover a broad spectrum of compounds in order to obtain a first crude estimate of the permeability coefficient for any compounds (see discussion at the end of Chapter 5).
- Theoretical skin permeability models are physiologically based and deduced after making assessments of the contributions of the possible routes of penetration through the skin and the interactions of the constituent materials of these routes with the permeating chemicals. Some models might describe the percutaneous absorption of certain classes of chemicals better than others, depending on the assumptions regarding the skin structure and composition as they affect the percutaneous absorption process.

These two types of models are described in this section, together with the assumptions and limitations of their validity and accuracy in predicting permeability coefficients and fluxes of water-borne contaminants.

5.2.1. Empirical Correlations

The skin's physico-chemical characteristics, as described in Chapters 2 and 3, determine the limits of percutaneous absorption of chemicals from contaminated water. As a vehicle, water hydrates the skin, which may itself enhance absorption through the skin. Clearly, the aqueous solubility of a pollutant sets the upper limit on the obtainable driving force for its diffusion, ΔC, and thus sets the upper limits on both the absorption rate and dose. Relative solubility (partitioning) of the contaminants between water and skin, and between the skin and the systemic circulation, also governs the overall absorption of the chemicals into the body, as partitioning sets the steepness of the concentration gradients across critical tissues. Other physico-chemical attributes of the pollutants define their interactions with the various skin components, thereby determining the ease of diffusion of solutes through the skin's barrier phases.

Scheuplein (1965, 1967) and Scheuplein and Blank (1971, 1973) were the first to introduce anatomically based physico-chemical models describing percutaneous absorption. Subsequently, Flynn (1990, 1991) proposed the following working model of the skin to assess the permeation of chemicals from their physico-chemical properties. The skin's two main layers are the epidermis and the dermis. The stratum corneum, the thin, outer dead layer of the epidermis, is the main barrier to percutaneous absorption of most chemicals. The stratum corneum is composed of sheets of acutely flattened cells packed full with the semi-crystalline protein, keratin, and held together with desmosomal anchorages. A cementing lipoidal substance fills the interstitial space between these building blocks. Keratin occupies about 65% and lipids occupy 25% of the total stratum corneum mass. Flynn (1989, 1990, 1991) offers the point of view that penetrants diffuse across this microscopically and macroscopically heterogeneous structure by distinct pathways which afford both non-polar and polar solutes access to the living tissues. For the most part, data from many sources indicate that the stratum corneum behaves, at least to a first approximation, as a hydrophobic barrier, seemingly establishing the importance of its intercellular lipids as a transport medium. However, the location of the polar pathway is uncertain, and recently its existence has even been called into question (Guy and Hadgraft, 1988; Potts and Guy, 1992). There is some evidence suggesting that highly polar compounds are held back (e.g., sugars, nucleosides, and ions). Presumably this is because they have extreme difficulty partitioning into and thereby passing through cell membranes (Flynn, 1991). However, this only becomes relevant under a damaged or denuded skin surface, otherwise the stratum corneum is the controlling element in absorption. Highly nonpolar compounds encounter similar difficulty, but in their case, passage across the watery domains of the viable epidermis is restrictive. In this instance, the viable tissue resistance may actually supersede that of the intact stratum corneum because, as the partition coefficient rises, the stratum corneum resistance decreases in direct proportion. Generally, permeability coefficients through denuded epidermis are estimated to lie somewhere between 0.03 and 1.0 cm/hour, depending on molecular size.

Flynn (1985, 1989) examined data on the in vitro permeation of organic compounds, both large and small, polar and nonpolar (including homologous alkanols, the 21-n-alkyl esters of hydrocortisone, and the 5'-n-alkyl esters of vidarabine in which polarity shifts are systematic and progressive) from aqueous media through hairless mouse skin as a function of the ether/water partition coefficients of the compounds. In the analysis, several zones of permeability behavior structured around either the ether/water or the octanol/water partition coefficients of the compounds were identified. For molecules in the nonpolar extreme, such as n-alcohols of chain length longer than about six, the more hydrophobic phenols, and the 21-hexanoate and 21-heptanoate esters of hydrocortisone, the indications are that the process of skin permeation is controlled in large part by the viable tissue barrier of the skin lying immediately beneath the stratum corneum. Here permeability coefficients on the order of 0.1 cm/hour are found in agreement with the estimated upper limit of permeability given in the previous section. For middle chain length alkanols, the more polar phenols, and the shorter hydrocortisone esters, log K_p is directly proportional to log $K_{o/w}$ (or its rough equivalent, alkyl chain length), meaning permeation is responsive to partitioning. Therefore, permeation must involve passage through a lipoidal medium which, given all other evidence concerning the skin barrier, would appear to be the interstitial lipid of the stratum corneum. This partitioning sensitive regime includes chemicals with values of log $K_{o/w}$ roughly ranging from - 0.5 ($K_{o/w} < 1.0$) up to 3.0 ($K_{o/w} > 1{,}000$).

For highly polar molecules such as water, methanol, ethanol, vidarabine, and all its 5′ esters to an alkyl chain length of eight, permeability coefficients again seem insensitive or at least less sensitive to partitioning influences. For hairless mouse skin, when log $K_{o/w} < -0.5$, then log K_p is on the order of - 5 (or K_p is on the order of 1×10^{-5} cm/hour). The comparable value of K_p for human skin is suggested to be as much as an order of magnitude lower (Flynn, 1985). For all these nonelectrolytes, a size effect was noted; small molecules permeate faster than large ones. Weak electrolytes (organic salts) exhibit pH dependent skin permeation behaviors, with K_p dropping off several orders of magnitude over the pH range where ionization occurs. Free (non-ionized) species is always a better skin penetrant than its corresponding ionized form irrespective of whether the compound is a weak acid or weak base. Consequently, weak acids exhibit their highest flux at a low pH, while weak bases exhibit theirs at a high pH. In either instance, the upper, limiting flux is displaced conspicuously, left or right, respectively, along the pH axis from the pK_a. The displacement can be several pH units large depending on the intrinsic lipophilicity of the undissociated species.

Fundamental membrane transport mechanics for any membrane can be inferred from general patterns of permeability. Truly porous membranes, for instance, enable free (non-ionized) and ionic species of weak electrolytes to permeate with equal facility, while simple isotropic lipid membranes allow the permeation of undissociated species only and exhibit a striking dependency on $K_{o/w}$. If ionic species permeate lipid membranes at all, they do so only as ion pairs and not as free ions. In the instance of the skin, there is a marked pH dependency to the permeation process and the fluxes of dissociated, ionic forms are several log orders less than the fluxes of free species at the same concentration. Still, some ions do pass through, which is one bit of evidence suggesting a polar pathway, albeit a minor one, through the stratum corneum.

Following up on these ideas, Flynn and Stewart (1988) developed an empirical algorithm for obtaining order of magnitude estimates of the permeability coefficients of drug compounds from their octanol/water partition coefficients. The intent of the algorithm was to provide a central estimate of K_p, not a high, safe estimate as would be needed for risk assessment. For this purpose, the upper and lower bounds on K_p values of compounds based on their relative polarities expressed in terms of log $K_{o/w}$ were formalized. Three regimes of permeability emerged from this evaluation. For highly polar compounds (log $K_{o/w} < -2.301$), a lower bound of 10^{-6} cm/hour was given to K_p. Compounds with log $K_{o/w}$ values lying between -2.301 and + 2.000 were assigned K_p values based on the partition coefficient using the relationship $\log K_p = \log K_{o/w} - 3.698$. The upper limit for the highly lipophilic compounds (log $K_{o/w} > 2$) was taken to be 10^{-2} cm/hour.

In a later publication, Flynn (1990) applied the same type of analytical approach to permeability data for human skin. Permeability coefficients and associated $K_{o/w}$ values were compiled for about 100 compounds (many of which were drugs) from the literature. Their K_p values were then examined with respect to corresponding $K_{o/w}$ (octanol/water) values and molecular weights (Table 5-4). Two groupings of the K_p's were designated as a function of molecular weight and the algorithms listed in Table 5-5 were proposed for estimating the permeability coefficients in human skin as a function of $K_{o/w}$. Though it had previously been recognized that skin permeability coefficients should vary systematically with molecular weight, this work provided an initial attempt to capture the molecular weight dependency within a predictive method of estimating permeability coefficients. It is noteworthy that a similar predictive absorption algorithm was proposed in a poster by Vanderslice and Ohanian (R.R. Vanderslice and E.V. Ohanian. Dermal absorption of drinking water contaminents, presented at the Society of Toxicology Meeting in Atlanta, GA, 1989.) for drinking water contaminants.

Table 5-4. Permeability Coefficients for Human Skin (Aqueous Solutions) and Octanol/Water Partition Coefficients (Neat) of Organic Compounds:

Alphabetical Ordering of Compounds Having Published Permeability Coefficients

Compound	Molecular Weight	K_p (cm/hr)	log K_p	log $K_{o/w}$
Aldosterone	360.44	3.0×10^{-6}	-5.52	1.08
Amobarbital	226.27	2.3×10^{-3}	-2.64	1.96
Atropine	289.38	8.5×10^{-6}	-5.07	1.81
Barbital	184.19	1.1×10^{-4}	-3.95	0.65
Benzyl alcohol	108.13	6.0×10^{-3}	-2.22	1.10
4-Bromophenol	173.01	3.6×10^{-2}	-1.44	2.59
2,3-Butanediol	90.12	4.0×10^{-5}	-4.40	-0.92
Butanoic acid (butyric acid)	88.10	1.0×10^{-3}	-3.00	0.79
n-Butanol	74.12	2.5×10^{-3}	-2.60	0.88
2-Butanone	72.10	4.5×10^{-3}	-2.35	0.28
Butobarbital	212.24	1.9×10^{-4}	-3.71	1.65
4-Chlorocresol	142.58	5.5×10^{-2}	-1.26	3.10
2-Chlorophenol	128.56	3.3×10^{-2}	-1.48	2.15
4-Chlorophenol	128.56	3.6×10^{-2}	-1.44	2.39
Chloroxylenol	156.61	5.2×10^{-2}	-1.28	3.39
Chlorpheniramine	274.80	2.2×10^{-3}	-2.66	?
Codeine	299.30	4.9×10^{-5}	-4.31	0.89
Cortexolone (11-desoxy-17-hydroxycorticosterone)	346.45	7.4×10^{-5}	-4.13	2.52
Cortexone (deoxycorticosterone)	330.45	4.5×10^{-4}	-3.35	2.88

Table 5-4. (continued)

Compound	Molecular Weight	K_p (cm/hr)	log K_p	log $K_{o/w}$
Corticosterone	346.45	$6.0\text{x}10^{-5}$	-4.22	1.94
Cortisone	360.46	$1.0\text{x}10^{-5}$	-5.00	1.42
o-Cresol	108.14	$1.6\text{x}10^{-2}$	-1.80	1.95
m-Cresol	108.14	$1.5\text{x}10^{-2}$	-1.82	1.96
p-Cresol	108.14	$1.8\text{x}10^{-2}$	-1.75	1.95
n-Decanol	158.28	$7.9\text{x}10^{-2}$	-1.10	4.00
2,4-Dichlorophenol	127.55	$6.0\text{x}10^{-2}$	-1.22	3.08
Diethylcarbamazine	199.29	$1.3\text{x}10^{-4}$	-3.89	?
Digitoxin	764.92	$1.3\text{x}10^{-5}$	-4.89	1.86
Ephedrine	165.23	$6.0\text{x}10^{-3}$	-2.22	1.03
B-estradiol	272.37	$3.0\text{x}10^{-4}$	-3.52	2.69
B-estradiol (2)	272.37	$5.2\text{x}10^{-3}$	-2.28	2.69
Estriol	288.37	$4.0\text{x}10^{-5}$	-4.40	2.47
Estrone	270.36	$3.6\text{x}10^{-3}$	-2.44	2.76
Ethanol	46.07	$7.9\text{x}10^{-4}$	-3.10	-0.31
2-Ethoxy ethanol (Cellosolve)	90.12	$2.5\text{x}10^{-4}$	-3.60	-0.54
Ethyl benzene	106.20	1.2	0.08	3.15
Ethyl ether	74.12	$1.6\text{x}10^{-2}$	-1.80	0.83
4-Ethylphenol	122.17	$3.5\text{x}10^{-2}$	-1.46	2.40
Etorphine	411.50	$3.6\text{x}10^{-3}$	-2.44	1.86
Fentanyl	336.50	$5.6\text{x}10^{-3}$	-2.25	4.37

Table 5-4. (continued)

Compound	Molecular Weight	K_p (cm/hr)	log K_p	log $K_{o/w}$
Fentanyl (2)	336.50	$1.0x10^{-2}$	-2.00	4.37
Fluocinonide	494.55	$1.7x10^{-3}$	-2.77	3.19
Heptanoic acid (enanthic acid)	130.18	$2.0x10^{-2}$	-1.70	2.50
n-Heptanol	116.20	$3.2x10^{-2}$	-1.50	2.72
Hexanoic acid (caproic acid)	116.16	$1.4x10^{-2}$	-1.85	1.90
n-Hexanol	102.18	$11.3x10^{-2}$	-1.89	2.03
Hydrocortisone	362.47	$3.0x10^{-6}$	-5.52	1.53
Hydrocortisone (2)	362.47	$1.2x10^{-4}$	-3.93	1.53
[Hydrocortisone-21-yl]-N,N dimethyl succinamate	489.60	$6.8x10^{-5}$	-4.17	2.03
[Hydrocortisone-21-yl]-hemipimelate	504.60	$1.8x10^{-3}$	-2.75	3.26
[Hydrocortisone-21-hemisuccinate	462.50	$6.3x10^{-4}$	-3.20	2.11
[Hydrocortisone-21-yl]-hexanoate	460.60	$1.8x10^{-2}$	-1.75	4.48
[Hydrocortisone-21-yl]-6-hydroxy hexanoate	476.60	$9.1x10^{-4}$	-3.04	2.79
[Hydrocortisone-21-yl]-octanoate	488.70	$6.2x10^{-2}$	-1.21	5.49
[Hydrocortisone-21-yl]-pimelamate	503.60	$8.9x10^{-4}$	-3.05	2.31
[Hydrocortisone-21-yl]-proprionate	418.50	$3.4x10^{-3}$	-2.47	3.00
[Hydrocortisone-21-yl]-succinamate	461.60	$2.6x10^{-5}$	-4.59	1.43
Hydromorphone	285.30	$1.5x10^{-5}$	-4.82	1.25
Hydroxypregnenolone	330.45	$6.0x10^{-4}$	-3.22	3.00
17a-Hydroxyprogesterone	330.45	$6.0x10^{-4}$	-3.22	2.74
Isoquinoline	129.15	$1.7x10^{-2}$	-1.78	2.03

Table 5-4. (continued)

Compound	Molecular Weight	K_p (cm/hr)	log K_p	log $K_{o/w}$
Meperidine	247.00	3.7×10^{-3}	-2.43	2.72
Methanol	32.04	5.0×10^{-4}	-3.30	-0.77
Methyl-[hydrocortisone-21-yl]-succinate	476.60	2.1×10^{-4}	-3.68	2.58
Methyl-[hydrocortisone-21-yl]-pimelate	518.60	5.4×10^{-3}	-2.27	3.70
Methyl-4-hydroxy benzoate	152.14	9.1×10^{-3}	-2.04	1.96
Morphine	285.30	9.3×10^{-6}	-5.03	0.62
2-Naphthol	144.16	2.8×10^{-2}	-1.55	2.84
Naproxen	230.26	4.0×10^{-4}	-3.40	3.18
Nicotine	162.23	1.9×10^{-2}	-1.71	1.17
Nitroglycerine	227.09	1.1×10^{-2}	-1.96	2.00
3-Nitrophenol	139.11	5.6×10^{-3}	-2.25	2.00
4-Nitrophenol	139.11	5.6×10^{-3}	-2.25	1.96
N-Nitrosodiethanolamine	134.13	6.0×10^{-6}	-5.22	?
n-Nonanol	144.26	6.0×10^{-2}	-1.22	3.62
Octanoic acid (caprylic acid)	144.21	2.5×10^{-2}	-1.60	3.00
n-Octanol	130.23	5.2×10^{-2}	-1.28	2.97
Ouabain	584.64	7.8×10^{-7}	-6.11	?
Pentanoic acid (valeric acid)	102.13	2.0×10^{-3}	-2.70	1.30
n-Pentanol	88.15	6.0×10^{-3}	-2.22	1.56
Phenobarbital	232.23	4.6×10^{-4}	-3.34	1.47
Phenol	94.11	8.1×10^{-3}	-2.09	1.46

Table 5-4. (continued)

Compound	Molecular Weight	K_p (cm/hr)	log K_p	log $K_{o/w}$
Pregnenolone	316.47	1.5×10^{-3}	-2.82	3.13
Progesterone	314.45	1.5×10^{-3}	-2.82	3.77
n-Propanol	60.10	1.4×10^{-3}	-2.85	0.25
Resorcinol	110.11	2.4×10^{-4}	-3.62	0.80
Salcylic acid	138.12	6.3×10^{-3}	-2.20	2.26
Scopolamine	303.35	5.0×10^{-5}	-4.30	1.24
Styrene	104.10	6.5×10^{-1}	-0.19	2.95
Sucrose	342.30	5.2×10^{-6}	-5.28	-2.25
Sufentanyl	387.50	1.2×10^{-2}	-1.92	4.59
Testosterone	288.41	4.0×10^{-4}	-3.40	3.31
Thymol	150.21	5.2×10^{-2}	-1.28	3.34
Toluene	92.10	1.0	0.00	2.75
2,4,6-Trichlorophenol	162.00	5.9×10^{-2}	-1.23	3.69
Water	18.01	5.0×10^{-4}	-3.30	-1.38
3,4-Xylenol	122.17	3.6×10^{-2}	-1.44	2.35

Source: Flynn (1990)

Table 5-5. Algorithms for Calculating Permeability Coefficients from Octanol/Water Coefficients[a]

	Low Molecular Weight Compounds (< 150)	High Molecular Weight Compounds (> 150)
$\log K_{o/w} < 0.5$	$\log K_p = -3$	$\log K_p = -5$
$0.5 \leq \log K_{o/w} \leq 3.0$	$\log K_p = -3.5 + \log K_{o/w}$	
$0.5 \leq \log K_{o/w} \leq 3.5$		$\log K_p = -5.5 + \log K_{o/w}$
$\log K_{o/w} > 3.0$	$\log K_p = -0.5$	
$\log K_{o/w} > 3.5$		$\log K_p = -1.5$

[a] Where K_p = Permeability Coefficient.

Source: Flynn (1990)

Regression equations for the prediction of K_p values for skin from partition coefficients and/or molecular weight values have long been available, but generally these were developed for specific sets or classes of compounds. For instance, Lien and Tong (1973) re-evaluated data of Treherne (1956) dealing with permeation of a small, but diverse group of nonelectrolytes through rabbit skin and dermis in vitro. Scheuplein (1965) studied aliphatic alcohols passing through human epidermis in vitro, while Scheuplein and his coworkers (1969) measured the permeation of steroids through human epidermis in vitro. Stoughton et al. (1960) considered the vasoactivity of nicotinic acid derivatives in situ and developed several empirical relationships for the evaluation of the permeability coefficients from these data. Guy and Hadgraft (1989b) summarized these experimental data and derived empirical structure-activity correlations for the following chemical classes: alkanoic acids (Liron and Cohen, 1984a,b); alkanols (Behl et al., 1980; Scheuplein and Blank, 1971); nicotinic acid esters (Houk and Guy, 1988; Stoughton et al., 1960); nonsteroidal anti-inflammatory drugs (Yano et al., 1986); phenols (Houk and Guy, 1988; Roberts et al., 1977); phenylboronic acids (Clendenning and Stoughton, 1962); polynuclear aromatics (Roy et al., 1987); and steroids (Idson and Behl, 1987; Scheuplein et al., 1969). In addition, Tsuruta (1975a, 1982) reported a good correlation between the aqueous solubilities of compounds and the absorption rates of aliphatic and aromatic hydrocarbons. Table 5-6 summarizes the classes of chemicals and the physico-chemical properties that have been correlated with permeability coefficients.

Since all the relationships found in Table 5-6 were derived empirically from compounds in narrowly defined structural classes, the generality of their use must be questioned. In other words, they have no global predictive value. Guy and Hadgraft (1989b) explored the validity of using the regression equation derived empirically for one class of compounds under a set of defined experimental conditions to predict the K_p values for a compound in a structurally dissimilar class. They found that when the K_p values for phenols are compared to the predictions obtained by the equation developed by Lien and Tong (1973) for alkanols, there is a tendency to overestimate the absorption values for the phenols, with the most marked deviation in predictions of K_p for phenols with log $K_{o/w} < 2.0$. Despite such shortcomings, analyses as found in Table 5-6 are important in that they give a consistent view of the high degree of correlation of skin permeability with lipophilicity.

5.2.2. Theoretical Skin Permeation Models

Carefully constructed, anatomically based, physical models provide an alternative to the strictly empirical approaches for obtaining K_p values. Scheuplein and co-workers (1965, 1968, 1971), Michaels et al. (1975), Albery and Hadgraft (1979), Berner and Cooper (1987), and Kasting et al. (1987) all developed models of this kind, each differing in the description of the transport phases of the skin. One anticipates that, following further research, a comprehensive model of this kind will evolve which is generally useful for estimating permeability coefficients. Therefore, this approach to model construction offers the scientific community its best hope for forecasting permeability coefficients from known physico-chemical characteristics of permeants. The earliest models are described in very general terms below, mostly without their associated equations. The latter were omitted because certain critical information needed to implement the predictive use of each of the equations is nonexistent. For the most part, these models have been used only to correlate sets of experimental K_p values of drugs (Michaels et al., 1975; Osborne, 1986) with certain physico-chemical properties, with model parameters being drawn from best fits of experimental data to the theoretical expectations. However, once refined, models as these should be useful for predicting K_p's not only of drugs but of environmental pollutants as well (Brown et al., 1990).

Table 5-6. Regression Equations Developed by Various Authors

Chemical Class	Experimental System	Percutaneous Absorption Function	Reference	
			Data	Equation
Aliphatic alcohols: water (sic) methanol ethanol n-propanol n-butanol n-pentanol n-hexanol n-heptanol n-octanol	Human epidermis in vitro	$\log K_p$ (cm/hr) = 0.420 $\log K_o$ -2.354 $\log K_p$ (cm/hr) = 0.544 $\log K_{o/w}$ -2.884 $\log K_p$ (cm/hr) = 0.934 $\log K_{sc/w}$ -2.891 K_o: olive oil/water partition coefficient $K_{o/w}$: octanol/water partition coefficient $K_{sc/w}$: stratum corneum/water partition coefficient	Scheuplein (1966)	Lien and Tong (1973)
	Full thickness hairless mouse in vitro; same chemicals as Scheuplein (1966)	$\log K_p$ = 0.50 $\log K_{o/w}$ -2.52	Behl et al. (1980)	Guy and Hadgraft (1989b)

Table 5-6. (continued)

Chemical Class	Experimental System	Percutaneous Absorption Function	Reference	
			Data	Equation
Phenols: resorcinol *p*-nitrophenol *m*-nitrophenol phenol methyl hydroxybenzoate *m*-cresol *o*-cresol *p*-cresol β-naphthol *o*-chlorophenol *p*-ethylphenol 3,4-xylenol *p*-bromophenol *p*-chlorophenol thymol chlorocresol chloroxylenol 2,4,6-trichlorophenol 2,4-dichlorophenol	Human epidermis in vitro	$\log K_p = -0.36 (\log K_{o/w})^2 + 2.39 (\log K_{o/w}) - 5.2$	Roberts et al. (1977)	Guy & Hadgraft (1989b)

Table 5-6. (continued)

Chemical Class	Experimental System	Percutaneous Absorption Function	Reference	
			Data	Equation
Phenols and esters of nicotinic acid: resorcinol catechol *p*-methoxyphenol phenol *p*-cresol *p*-bromophenol *p*-iodophenol 4-chloro-*m*-cresol *n*-butylphenol *n*-pentylphenol methyl nicotinate ethyl nicotinate *n*-butyl nicotinate *n*-pentyl nicotinate *n*-hexyl nicotinate	Ispropyl myristate membrane (IPM)	$\log K_p = -0.48 (\log K_{o/w})^2 + 2.32 (\log K_{o/w}) - 2.2$	Houk and Guy (1988)	Guy and Hadgraft (1989b)
	Tetradecane membrane (TD)	$\log K_p = -0.40 (\log K_{o/w})^2 + 2.55 (\log K_{o/w}) - 4.0$	Houk and Guy (1988)	Guy and Hadgraft (1989b)
Phenylboronic (P) acids: m-carbamido-P m-carboxy-P p-carbonxy-P m-amino-P p-methoxy-P P p-chloro-P p-methyl-P	Human skin in vitro	$\log C = 0.573 (\log K_{o/w}) - 3.749$ $\log C = 0.212 (\log K_{o/w})^2 + 1.133 (\log K_{o/w}) - 3.999$ $\log C = 0.417 (\log K_{b/w}) - 2.463$ $K_{o/w}$: octanol/water partition coefficient $K_{b/w}$: benzene/water partition coefficient C: molar concentration to cause a standard biological response (i.e., boron penetration into the dermis).	Clendenning and Stoughton (1962)	Lien and Tong (1973)

Table 5-6. (continued)

Chemical Class	Experimental System	Percutaneous Absorption Function	Reference	
			Data	Equation
Nonelectroyltes: ethyl iodide methanol ethanol thiourea glycerol urea glucose	Rabbit whole skin in vitro	$\log K_p$ (cm/hr) = $-1.006 \log MW -1.371$ $\log K_p$ (cm/hr) = $-1.836 \log MR_d -0.982$ $\log K_p$ (cm/hr) = $0.392 \log K_{o/w} -2.761$ $\log K_p$ (cm/hr) = $-0.060 (\log K_{o/w})^2 +0.309 (\log K_{o/w}) -2.591$ $\log K_p$ (cm/hr) = $0.360 (\log K_{o/w}) -0.964 \log (MR_d)-1.599$ $\log K_p$ (cm/hr) = $0.385 (\log K_{o/w}) -0.856 \log MW-1.51$	Treherne (1956)	Lien and Tong (1973)
	Rabbit dermis in vitro	$\log K_p$ (cm/hr) = $0.100 (\log K_{o/w}) -0.970$ $\log K_p$ (cm/hr) = $-0.622 \log MR_d -0.395$ $\log K_p$ (cm/hr) = $-0.575 \log MW -0.098$ K_p = permeability constant MW = molecular weight MR_d = molar refractivities		

Table 5-6. (continued)

Chemical Class	Experimental System	Percutaneous Absorption Function	Reference	
			Data	Equation
Steroids: progesterone (Po) pregnenolone (Pe) hydroxy-Pe hychoxy-Po cortexone testosterone cortexolone corticosterone cortisone hydrocortisone aldosterone estrone estradiol estriol	Human epidermis in vitro	$\log K_p$ (cm/hr) = $0.818 \log K_{hex/w} - 3.556$ $\log K_p$ (cm/hr) = $1.262 \log K_{ac/w} - 5.211$ $\log K_p$ (cm/hr) = $2.626 \log K_{sc/w} - 7.537$ $\log K_p$ (cm/hr) = $0.891 \log K_{e/w} - 5.175$ $\log K_p$ (cm/hr) = $-0.207 \log (K_{e/w})^2 - 1.494 \log (K_{e/w}) - 5.425$ $K_{hex/w}$: hexadecane/water partition coefficient $K_{ac/w}$: amyl caproate/water partition coefficient $K_{sc/w}$: stratum corneum/water partition coefficient $K_{e/w}$: ether/water partition coefficient	Scheuplein et al. (1969)	Lien and Tong (1973)
hydrocortisone and 21-esters (acetate through heptanoate)	Hairless mouse skin in vitro	$\log K_p = 0.56 \log K_{e/w} - 3.39$	Idson and Behl (1987)	Guy and Hadgraft (1989b)

Table 5-6. (continued)

Chemical Class	Experimental System	Percutaneous Absorption Function	Reference	
			Data	Equation
Nonsterioidal anti-inflammatory drugs (NSAIDSs): alclofenac aspirin bufexamac flufenamic acid flurbiprofen iboprofen indomethacin naproxen salicylic acid methylsalicylate ethylsalicylate *n*-propylsalicylate *n*-butylsalicylate ethylene glycol monosalicylate salicylamide salicyluric acid	Human in vivo	$\log[\%\text{ dose absorbed}] = -0.23(\log K_{o/w})^2 + 1.14(\log K_{o/w}) + 0.42$	Yano et al. (1986)	Guy & Hadgraft (1989b)

Table 5-6. (continued)

Chemical Class	Experimental System	Percutaneous Absorption Function	Reference	
			Data	Equation
Nicotonic Acid esters: nicotonic acid (NA) NA-HCl methyl nicotinate ethyl nicotinate butyl nicotinate hexyl nicotinate octyl nicotinate tetrahydrofurfuryl nicotinate	Human skin in situ	$\log (1/C) = 1.008 \log K_{e/w} + 1.230 \log S + 6.604$ C: threshold molar concentration to induce visible erythema (skin reddening) $K_{e/w}$: ether/water partition coefficient S: molar solubility (mole/liter H_2O)	Stoughton et al. (1960)	Lien and Tong (1973)
Corticosteriods: prednisolone 9α-fluorohydrocortisone methylprednisolone hydrocortisone hydrocortisone acetate prednisolone actate dexamethasone 9α-fluorohydrocortisone acetate triamcinolone acetonide fluocinolone acetonide flurandrenolone acetonide		$\log 1/C = 2.553 \log K_{e/w} + 1.139 \log S + 6.101$ C: molar concentration to induce vasoconstriction	Katz and Shaikh (1965)	Lien and Tong (1973)

Table 5-6. (continued)

Chemical Class	Experimental System	Percutaneous Absorption Function	Reference	
			Data	Equation
Miscellaneous: barbitone phenobarbitone butobarbitone amylobarbitone hydrocortisone nicotine salicylic acid isoquinoline	Human Skin in vitro IPM } TD }	$\log K_p = 0.66 \log K_{t/w} - 2.02$ $K_{t/w}$: tetradecane/water partition coefficient $\log K_p = 0.71 \log K_{o/w} - 0.03$ (IPM: Isopropyl myristate membrane; TD: tetradecane membrane)	Hadgraft and Ridout (1987, 1988)	Guy and Hadgraft (1989b)

Table 5-6. (continued)

Chemical Class	Experimental System	Percutaneous Absorption Function	Reference	
			Data	Equation
Polynuclear aromatics (PNAs): 3-ring: acenaphthylene acenaphthene dibenzofuran fluorene 9,10-dihydrophenanthrene 1-methyl- fluorenenzothiophene dibenzothiophene phenanthrene anthracene carbazole 2-methylanthrcene 9,10-dimethylanthracene 1-methylphenanthrene 9-methylanthracene 3,6-dimethylphenanthrene 2-ethylanthracene 4- and 5-ring: fluoranthene pyrene 2,3-benzofluorene benz(a)anthracene chrysene benzo(k)fluoranthene benzo(e)pyrene benzo(a)pyrene	Rat skin in vitro	log (% applied dose) = f (log $K_{o/w}$)	Roy et al. (1987)	

Table 5-6. (continued)

Chemical Class	Experimental System	Percutaneous Absorption Function	Reference	
			Data	Equation
Pure straight-chain Alkanoic acids C_2-C_8: acetic acid propionic acid butyric acid pentanoic acid hexanoic acid heptanoic acid octanoic acid	Porcine skin in vitro	K_p inversely related to melting points.	Liron and Cohen (1984a,b)	Guy and Hadgrath (1989a)
Aliphatic and aromatic hydrocarbons: benzene toluene styrene ethylbenzene *o*-xylene *n*-pentane 2-methylpentane *n*-hexane *n*-heptane *n*-octane	Rat skin in vitro	$\log J = 1.41 \log S - 0.297$	Tsuruta (1982a)	Tsuruta (1982)

Table 5-6. (continued)

Chemical Class	Experimental System	Percutaneous Absorption Function	Reference	
			Data	Equation
Aliphatic hydrocarbons: 1,2-dichloroethane tetrachloroethylene 1,1,2,2-tetra-chloroethane trichloromethane 1,1,2-trichloroethane dichloromethane 1,1,1-trichlorethane trichloroethylene	Mice in vitro	Percutaneous absorption rate (nM/min/cm^2 of skin) as a function of solubility in water: $S \leq 16$ (mM at 25°C) $J = 30.8 + (2.13)S \quad r = 0.87$ $S \leq 16$ $J = -52.8 + (6.59)S \quad r = 1.00$	Tsuruta (1975)	Tsuruta (1975)

5.2.2.1. *Scheuplein Laminate Model with Parallel Follicular Pathway*

Scheuplein and co-workers (1965, 1968, 1971) were the first to attempt an anatomically based depiction of the skin barrier. They viewed permeability of the epidermis as a two-step process involving transport across the stratum corneum and then transport across the living epidermal tissue beneath. A parallel, independent follicular pathway bypassing the stratum corneum was also built into the model, to help explain the efficacy of topically applied drugs under circumstances where the lag time for diffusion is measured in whole days, but the therapeutic response is prompt. In this model the stratum corneum, though admittedly a lipoprotein mosaic, was assigned a uniform diffusion property. Using alkanols as test permeants, Scheuplein and co-workers were able to demonstrate the partitioning dependency of skin permeability with a refreshing clarity and also, for the first time, establish the role of the viable tissue beneath the stratum corneum as a limiting barrier at high permeant lipophilicity. K_p was expressed in simple terms, i.e., $K_{sc/w}D_{sc}/l_{sc}$ and the first attempts ever were made to experimentally determine values for $K_{sc/w}$.

5.2.2.2. *Michaels' Two-Phase Model for Stratum Corneum*

Michaels et al. (1975) presented a conceptual model for skin permeability that describes K_p in terms of the two-phase, "brick-and-mortar" structure of the stratum corneum illustrated in Figure 2-2. This model, too, was an early attempt to relate the absorption of compounds through the skin to their physico-chemical properties and diffusivities within the respective phases of the skin. It was presumed that molecules passively diffuse through the stratum corneum by dissolving either in its keratin or its lipid phase. Diffusivities in the lipoidal and proteinaceous phases of the stratum corneum were explicitly accounted for as the lipid phase/protein phase partition coefficient. To actually use the model, however, one needs to have exact information concerning the ultra-structure of the stratum corneum and other details of its macroscopic organization, facts which are simply unavailable; thus the model serves more as a conceptual tool than as a tool for forecasting K_p's. Notably, when fitting data to the model, Michaels et al. (1975) used mineral oil/water partition coefficient values to approximate the lipid/protein phase partition coefficient of the compounds; Brown et al. (1990) suggests that the more readily available octanol/water partition coefficients serve the same purpose.

5.2.2.3. Two Parallel Pathway Model

A model proposed by Berner and Cooper (1987) which assigns parallel lipoidal and polar pathways to the stratum corneum is conceptually similar to the model proposed by Michaels et al. (1975). Assuming that the fluxes through the polar and lipophilic pathways are independent and additive, K_p can be estimated from this model providing appropriate information is available for the area fractions of the two pathways (A_P and A_L), and for the corresponding diffusion coefficients (D_P and D_L). A value for the effective thickness of the stratum corneum, l_{sc}, is also required. Berner and Cooper proposed values of 0.1 and 0.9 for A_P and A_L, but clearly these lack an adequate physiological basis. Similar to Michaels et al. (1975), Berner and Cooper (1987) used mineral oil/water partition coefficients in their analysis. Again, Brown et al. (1990) have made the point that the substitution of readily available $K_{o/w}$ values appears to be without effect on the predictive capability of the model. The molecular weight of a permeant was also explicitly considered.

Berner and Cooper (1987) subsequently added a third pathway to the model. Specifically, a heterogeneous oil-water multi-laminate pathway was added to the distinct polar and nonpolar routes of the original model. Because this heterogeneous pathway model is difficult to solve, they developed equations to predict upper- and lower-bound K_p values of the model. Parameter values for the model were generally kept the same as before, except A_p and A_L were set at 0.5.

5.2.2.4. Albery and Hadgraft Model

Another model accounting for diffusive penetration of skin by multiple pathways, in this instance transcellular (protein) and intercellular (lipid) pathways across the stratum corneum, was developed by Albery and Hadgraft (1979). Area fractions for the specific routes were again invoked, and diffusion coefficients for each path were specified. These workers assigned values of one to the transcellular route area fraction and 7×10^{-6} to the area fraction of the intercellular route. These values seem far more physiologically likely than those employed by Berner and Cooper (1987). Diffusion coefficients given to the transcellular and intercellular routes were 1.9×10^{-6} cm^2/hour and 9.7×10^{-4} cm^2/hour, respectively.

5.2.2.5. *Kasting, Smith, and Cooper Model*

Kasting et al. (1987) have also contributed to the development of percutaneous absorption models. Like the others, they treat skin permeation as a simple passive diffusion process and, following Scheuplein, the stratum corneum is treated as if it were a homogeneous membrane responsible for the bulk of the barrier function of the skin. The starting point for this theory is Fick's first law for steady-state flux (J_{ss}) as expressed in Equation (4.10), which is based on an homogeneous membrane of thickness l_m, and on the intra-membrane concentration. The theory is based on the rationale that it would be easier to compare maximum penetration rates from saturated solutions than to try to ensure that the concentration at the boundary of the membrane is the same for all compounds. Diffusion coefficients of the form:

$$D = D^o \exp(-\beta\, v) \tag{5.1}$$

were introduced into the model, where the term ν is the van der Waals volume of the permeant and D^o and β are properties of the skin. Thus, this model is another that incorporates molecular size explicitly, in this instance, in terms of a molecular volume calculated from atomic radii. This model of the diffusion coefficient assumes that the stratum corneum lipids form a structured membrane regime with defined thermal transitions.

After substituting the expression for D into the maximum flux equation and rearranging the equation, the following expression was obtained:

$$\log\left[\frac{J_{\max}}{C_v^{sat}}\right] = \log\left[\frac{D^o}{l_{sc}}\right] - \frac{\beta}{2.303}\, v \tag{5.2}$$

Kasting et al. (1987) then measured steady-state skin penetration rates for 35 chemicals from saturated propylene glycol solutions and fitted these flux data to the above equation to get the following equation:

$$\log\left[\frac{J_{max}}{C_v^{sat}}\right] = 1.129 - 0.00812\ v \tag{5.3}$$

The most important contribution of this model is in the manner in which the molecular size dependency is stated.

5.2.3. Statistical Algorithms for K_p Based on Literature Data

The anatomically based, physical models presented previously are important because they place skin permeability in terms of its parallel pathways and series barriers. All have been fitted to data, but the data sets have been small. However, as a consequence of doing so, the dependency of permeability coefficients on lipophilicity of compounds is made unmistakenly evident. In addition, several models make a definite statement concerning a dependency of skin permeability on molecular size. This simultaneous dependency on both lipophilicity and molecular size was also accounted for by Flynn (1990) when treating the literature on permeability coefficients. Therefore, as a result of this confluence of developments, the data recently compiled by Flynn (1990) and listed in Table 5-4 have been subjected to independent statistical analyses by several investigators to find the goodness of fit of these data to equations accounting for both molecular size and polarity, the latter as determined by $K_{o/w}$. Three investigators independently worked the data along these lines.

Following Kasting et al. (1987), Potts and Guy (1992) fitted an equation, similar in form to Equation (5.2) to the permeability coefficient data:

$$\log\left[\frac{K_{p(est)}^{w}}{K_{o/w}}\right] = \log\left[\frac{D^{o}}{l_{sc}}\right] - \frac{\beta}{2.303}MW \tag{5.4}$$

and achieved the following relationship:

$$\log K^{w}_{p(est)} = -2.72 + 0.71 \log K_{o/w} - 0.0061\, MW \tag{5.5}$$

The squared multiple R of this fit is 0.67. This equation is an empirical statement that actually has solid theoretical underpinnings. Bronaugh and Barton (1991) used the same data set and successfully fitted a very similar regression line through the log K_p data as a function of molecular weight and log $K_{o/w}$. Equation (5.6) presents the outcome of this analysis:

$$\log K^{w}_{p(est)} = -2.61 + 0.67 \log K_{o/w} - 0.0061\, MW \tag{5.6}$$

The squared multiple R of this fit is 0.73. Remarkably, partitioning and molecular size alone explain about 70% of the variability in permeability coefficients, predicated by Equations (5.5) and (5.6). Flynn and Amidon (conversation between G.L. Flynn, University of Michigan, and K. Hoang, U.S. EPA, Office of Health and Environmental Assessment, Washington, DC, October, 1991) performed virtually the same statistical feat, with the exact same data. After exploring several possible expressions for the molecular weight dependency, Equation (5.7) was settled upon:

$$\log_e K^{w}_{p(est)} = -3.311 + 0.792 \log_e K_{o/w} - 1.45 \log_e MW \tag{5.7}$$

This equation has a multiple R value of 0.847 and a squared multiple R of 0.718. Moreover, adding crossterms like $\log_e K_{o/w}$ x $\log_e MW$ only marginally improve the correlation, suggesting that the dependencies on lipophilicity and molecular size are for the most part independent.

After independent statistical analyses of the data for organics in aqueous solution, Equation (5.5) by Potts and Guy (1992) was selected. This equation was used to generate the estimated $K^{w}_{p(est)}$ values in Table 5-7.

$$\log K_p = -2.72 + 0.71 \log K_{o/w} - 0.0061\ MW \tag{5.8}$$

Inspection of the inorganics listed in Table 5-3 indicates that most of them have values near 10^{-3} cm/hour and a few are lower. Accordingly, a default assumption of 10^{-3} cm/hour is recommended for inorganics that have not been tested.

The uncertainty in the predicted K_p's is judged to be within plus or minus one order of magnitude from the best fit value.

These procedures have been applied to over 200 compounds of environmental concern which were compiled across EPA programs. The predicted K_p values for these chemicals are listed in Table 5-7.

Table 5-7. Predicted K_p Estimates for Common Pollutants

Chemical	CAS No.	MWT	log K_{ow}	K_p (cm/hr)
Acetaldehyde	75070	44.1	-0.22	7.2e-04
Acetamide	60355	59.0	-1.26	1.1e-04
Acetylaminofluorene, 2-	53963	223.0	3.24	1.7e-02
Acrolein	107028	56.1	-0.10	7.4e-04
Acrylamide	79061	71.0	-0.67	2.4e-04
Acrylonitrile	107131	53.1	0.25	1.4e-03
Aldrin	309002	365.0	3.01	1.6e-03
Allyl chloride	107051	76.5	1.45	7.0e-03
1-Amino-2-methylanthraquinone	82280	237.3	2.80	6.6e-03
Aminoanthraquinone, 2-	117793	223.0	2.15	2.8e-03
Aminoazobenzene, p-	60093	197.0	2.62	8.7e-03
Aminoazotoluene, o-	97563	225.3	3.92	4.9e-02
Aminobiphenyl, 4-	92671	169.2	2.80	1.7e-02
Aniline	62533	93.1	0.90	2.2e-03
Anisidine, o-	90040	145.0	1.18	1.7e-03
Auramine	492808	267.4	3.54	1.5e-02
Benzo-b-fluoranthene	205992	252.3	6.12	1.2e+00
Benzene	71432	78.1	2.13	2.1e-02
Benzidine	92875	184.2	1.34	1.3e-03
Benzo-a-anthracene	56553	228.3	5.66	8.1e-01
Benzo-a-pyrene	50328	250.0	6.10	1.2e+00
Benzoic acid	65850	122.0	1.87	7.3e-03
Benzotrichloride	98077	195.0	2.92	1.5e-02
Benzyl chloride	100447	127.0	2.30	1.4e-02
Bis(2-chloroethyl)ether	111444	143.0	1.29	2.1e-03
Bromodichloromethane	75274	163.8	2.09	5.8e-03

Table 5-7. (continued)

Chemical	CAS No.	MWT	log K_{ow}	K_p (cm/hr)
Bromoform	75252	252.8	2.37	2.6e-03
Bromomethane	74839	95.0	1.19	3.5e-03
Bromophenol, p-	106412	173.0	2.65	1.3e-02
Butadiene, 1,3-	106990	54.0	1.99	2.3e-02
Butanediol, 2,3-	513859	90.1	-0.92	1.2e-04
Butanol, n-	71363	74.1	0.65	1.9e-03
Butoxyethanol, 2-	111762	118.0	0.83	1.4e-03
Captan	133062	300.0	2.35	1.3e-03
Carbon disulfide	75150	80.0	2.24	2.4e-02
Carbon tetrachloride	56235	153.8	2.83	2.2e-02
Chlordane	57749	409.8	5.54	5.2e-02
Chlordane (cis)	5103719	410.0	5.47	4.6e-02
Chlordane (trans)	5103742	410.0	5.47	4.6e-02
Chlorobenzene	108907	112.6	2.84	4.1e-02
Chlorocresol	59507	142.6	3.10	4.1e-02
Chlorodibromomethane	124481	208.3	2.23	3.9e-03
Chloroethane	75003	64.5	1.43	8.0e-03
Chloroform	67663	119.4	1.97	8.9e-03
Chloromethane	74873	50.5	0.91	4.2e-03
Chloromethyl methyl ether	107302	80.5	0.00	6.2e-04
Chlorophenol, o-	95578	128.6	2.16	1.1e-02
Chlorophenol, p-	106489	128.6	2.39	1.6e-02
Chlorothalonil	1897456	265.9	3.86	2.5e-02
Chloroxylenol		135.2		
Chrysene	218019	228.3	5.66	8.1e-01
Cresidine, p-	120718	137.2	1.67	4.3e-03

Table 5-7. (continued)

Chemical	CAS No.	MWT	log K_{ow}	K_p (cm/hr)
Cresol, m-	108394	108.1	1.96	1.0e-02
Cresol, o-	95487	108.1	1.95	1.0e-02
Cresol, p-	106445	108.1	1.94	1.0e-02
D&C Red No. 19	81889	479.0	0.00	2.3e-06
DDD	72548	320.0	5.80	2.8e-01
DDE	72559	318.0	5.69	2.4e-01
DDT	50293	355.0	6.36	4.3e-01
Decanol	112301	158.3	4.11	1.7e-01
Di-2-ethylhexyl phthalate	117817	391.0	5.11	3.3e-02
Diaminoanisole, 2,4-	615054	138.2	-0.12	2.3e-04
Diaminotoluene	95807	122.0	0.34	6.0e-04
Diaminotoluene, 2,4-	101804	200.0	2.06	3.3e-03
Dibenzo(a,h)anthracene	226368	278.4	6.84	2.7e+00
Dibutyl phthalate	84742	278.0	4.13	3.3e-02
Dichlorobenzene, 1,2-	95501	147.0	3.38	6.1e-02
Dichlorobenzene, 1,3-	541731	147.0	3.60	8.7e-02
Dichlorobenzene, 1,4-	106467	147.0	3.39	6.2e-02
Dichlorobenzidine, 3,3'	91941	253.1	3.51	1.7e-02
Dichlorodifluoromethane	75718	120.9	2.16	1.2e-02
Dichloroethane, 1,1-	75343	99.0	1.79	8.9e-03
Dichloroethane, 1,2-	107062	99.0	1.48	5.3e-03
Dichloroethylene, 1,1-	75354	96.9	2.13	1.6e-02
Dichloroethylene, 1,2-	156592	96.9	1.86	1.0e-02
Dichlorophenol, 2,4-	120832	163.0	2.92	2.3e-02
Dichloropropane, 1,2-	78875	113.0	2.00	1.0e-02
Dichloropropene, 1,3-	542756	111.0	1.60	5.5e-03

Table 5-7. (continued)

Chemical	CAS No.	MWT	log K_{ow}	K_p (cm/hr)
Dichlorvos	62737	221.0	1.47	9.5e-04
Dieldrin	60571	381.0	4.56	1.6e-02
Diepoxybutane	1464535	86.1	-1.84	2.8e-05
Diethyl phthalate	84662	222.0	2.47	4.8e-03
Diethyl sulfate	64675	154.0	1.14	1.4e-03
Dimethoxybenzidine, 3,3'-	119904	254.4	1.81	1.0e-03
Dimethyl phthalate	131113	194.0	1.56	1.6e-03
Dimethyl sulfate	77781	126.0	1.16	2.2e-03
Dimethylamine, n-nitroso-	62759	74.1	-0.57	2.7e-04
Dimethylaminoazobenzene, 4-	60117	225.0	4.58	1.4e-01
Dimethylbenzidine, 3,3'-	119937	212.3	2.34	4.4e-03
Dimethylcarbamyl chloride	79447	107.5	0.00	4.2e-04
Dimethylhydrazine, 1,1-	57147	60.0	-1.50	7.1e-05
Dimethylphenol, 2,4-	105679	122.2	2.30	1.5e-02
Dimethylphenol, 3,4-	95658	122.2	2.23	1.3e-02
Dinitrotoluene, 2,4-	121142	182.1	1.98	3.8e-03
Dinitrophenol, 2,4-	51285	184.1	1.54	1.8e-03
Dinitrotoluene, 2,6-	606202	182.1	1.72	2.5e-03
Dioxane, 1,4-	123911	88.1	-0.27	3.6e-04
Diphenylamine, n-nitroso-	86306	198.2	3.50	3.6e-02
Diphenylhydrazine, 1,2-	122667	184.2	2.94	1.8e-02
Dipropylamine, n-nitroso-	621647	130.2	1.36	2.8e-03
Endrin	72208	381.0	4.56	1.6e-02
Epichlorohydrin	106898	92.0	-0.21	3.7e-04
Ethanol	64175	46.0	-0.31	6.0e-04
Ethanol, 2-(2-butoxyethoxy)-	112345	162.0	-0.92	4.4e-05

Table 5-7. (continued)

Chemical	CAS No.	MWT	log K_{ow}	K_p (cm/hr)
Ethanol, 2-(2-ethoxyethoxy)-	111900	134.0	-0.08	2.5e-04
Ethanol, 2-(2-methoxyethoxy)-	111773	120.0	-0.42	1.8e-04
Ethoxyethanol, 2-	110805	90.0	-0.10	4.6e-04
Ethoxyethyl acetate, 2-	111159	132.0	0.65	8.6e-04
Ethyl acrylate	140885	100.0	1.32	4.0e-03
Ethyl carbamate	51796	89.0	-0.15	4.3e-04
Ethyl ether	60297	74.1	0.89	2.9e-03
Ethylbenzene	100414	106.2	3.15	7.4e-02
Ethylene oxide	75218	44.1	-0.30	6.3e-04
Ethylenedibromide	106934	188.0	1.96	3.3e-03
Ethyleneimine	151564	43.0	-1.12	1.7e-04
Ethylenethiourea	96457	96.0	-0.66	1.7e-04
Ethylphenol, p-	123079	120.0	2.26	1.4e-02
Fluoranthene	206440	202.3	4.95	3.6e-01
Formaldehyde	50000	30.0	0.35	2.2e-03
Glycerol	56815	92.1	-1.76	2.9e-05
Heptachlor	76448	373.5	4.27	1.1e-02
Heptanol	111706	116.0	2.41	1.9e-02
Hexachlorobenzene	118741	284.8	5.31	2.1e-01
Hexachlorobutadiene	87683	260.8	4.78	1.2e-01
Hexachloroethane	67721	236.7	3.93	4.2e-02
Hexamethylphosphoramide	680319	179.0	0.03	1.6e-04
Hexanol	111273	102.0	2.03	1.3e-02
Hydrazine/Hydrazine sulfate	302012	32.0	-2.07	4.1e-05
Indeno(1,2,3-CD)pyrene	193395	276.3	6.58	1.9e+00
Isophorone	78591	138.2	1.70	4.4e-03

Table 5-7. (continued)

Chemical	CAS No.	MWT	log K_{ow}	K_p (cm/hr)
Lindane	58899	291.0	3.72	1.4e-02
Maneb	12427382	265.3	0.00	4.6e-05
Mechlorethamine	51752	156.0	1.07	1.2e-03
Methanol	67561	32.0	-0.77	3.5e-04
Methoxyethanol, 2-	109864	76.0	-0.77	1.9e-04
Methoxypropan-2-ol, 1-	107982	90.0	-0.18	4.0e-04
Methyl ethyl ketone	78933	72.0	0.29	1.1e-03
Methyl hydroxybenzoate	99763	152.1	1.92	5.2e-03
Methyl iodide	74884	142.0	1.51	3.1e-03
Methylaziridine, 2-	75558	57.0	-0.60	3.2e-04
Methylene bis(2-chloroaniline), 4,4'-	101144	267.2	3.94	2.8e-02
Methylene bis(N,N'-dimethyl)aniline, 4,4'-	101611	254.0	4.75	1.3e-01
Methylene chloride	75092	84.9	1.25	4.5e-03
Methylenedianiline, 4,4'-	101779	198.0	1.59	1.6e-03
Michler's ketone	90948	268.4	4.07	3.4e-02
Mustard Gas	505602	159.1	2.03	5.6e-03
Naphthalene	91203	128.2	3.30	6.9e-02
Naphthol, b-	135193	144.2	2.84	2.6e-02
Naphthylamine, 1-	134327	143.2	2.25	1.0e-02
Naphthylamine, 2-	91598	143.2	2.28	1.1e-02
Nitrilotriacetic acid	139139	191.0	-0.18	9.7e-05
Nitro-o-anisidine, 5-	99592	152.7	1.47	2.5e-03
Nitrobiphenyl, 4-	92933	199.2	3.77	5.5e-02
Nitrofen	1836755	284.1	5.53	3.0e-01
Nitrophenol, 2-	88755	139.1	1.79	5.0e-03

Table 5-7. (continued)

Chemical	CAS No.	MWT	log K_{ow}	K_p (cm/hr)
Nitrophenol, 2-amino-4-	99570	154.1	1.36	2.0e-03
Nitrophenol, 3-	554847	139.1	2.00	7.1e-03
Nitrophenol, 4-	100027	139.1	1.91	6.1e-03
Nitrophenol, 4-amino-2-	119346	154.1	0.96	1.1e-03
Nitropropane, 2-	79469	110.0	0.55	1.0e-03
Nitroso-di-n-butylamine, n-	924163	158.2	1.92	4.8e-03
Nitroso-N-ethylurea, n-	759739	117.1	0.23	5.4e-04
Nitroso-N-methylurea, n-	684935	103.1	-0.03	4.3e-04
Nitrosodiethanolamine, n-	1116547	134.0	-1.58	2.2e-05
Nitrosodiethylamine, n-	55185	88.0	0.48	1.2e-03
Nitrosodiphenylamine, p-	156105	198.2	3.50	3.6e-02
Nitrosomethylvinylamine, n-	4549400	86.1	0.00	5.7e-04
Nitrosomorpholine, n-	59892	116.1	-0.44	1.8e-04
Nitrosonornicotine, n-	16543558	177.2	0.03	1.7e-04
Nitrosopiperidine, n-	100754	350.3	0.36	2.5e-05
Nonanol	143088	144.0	3.47	7.3e-02
Octanol	111875	130.0	2.97	3.9e-02
Parathion	56382	291.0	3.83	1.7e-02
PCB-chlorobiphenyl, 4-	2051629	292.0	6.50	1.3e+00
PCB-hexachlorobiphenyl	26601649	361.0	6.72	7.1e-01
Pentachloronitrobenzene	82688	295.3	4.64	5.9e-02
Pentachlorophenol	87865	266.4	5.86	6.5e-01
Pentanol	71410	88.0	1.56	7.1e-03
Pentanone, 4-methyl-2-	108101	100.0	1.19	3.3e-03
Phenanthrene	85018	178.2	4.57	2.7e-01
Phenol	108952	94.0	1.46	5.5e-03

Table 5-7. (continued)

Chemical	CAS No.	MWT	log K_{ow}	K_p (cm/hr)
Phenol, 4,6-dinitro-2-methyl-	534521	198.1	2.12	3.8e-03
Propanol	71238	60.0	0.30	1.3e-03
Propiolactone, beta-	57578	575.8	-0.46	3.3e-04
Propylene oxide	75569	58.1	0.03	8.9e-04
Resorcinol	108463	110.1	0.80	1.5e-03
Safrole	94597	162.2	2.66	1.5e-02
Styrene	100425	104.1	2.95	5.5e-02
Styrene oxide	96093	120.0	1.61	4.9e-03
TCDD	1746016	322.0	6.80	1.4e+00
Tetrachlorethylene	127184	165.8	3.40	4.8e-02
Tetrachloroethane, 1,1,2,2-	79345	167.9	2.39	9.0e-03
Thioacetamide	62555	75.0	0.71	2.1e-03
Thiodianiline, 4,4'-	139651	216.0	2.03	2.5e-03
Thiourea	62566	76.0	-0.95	1.4e-04
Thymol	89838	150.2	3.30	5.1e-02
Toluene	108883	92.1	2.73	4.5e-02
Toluidine hydrochloride, o-	636215	143.2	0.00	2.1e-03
Toluidine, o-	95534	107.0	1.32	3.7e-03
Toxaphene	8001352	414.0	4.82	1.5e-02
Trichlorobenzene, 1,2,4-	120821	181.5	3.98	1.0e-01
Trichloroethane, 1,1,1-	71556	133.4	2.49	1.7e-02
Trichloroethane, 1,1,2-	79005	133.4	2.05	8.4e-03
Trichloroethylene	79016	131.4	2.42	1.6e-02
Trichlorofluoromethane	75694	137.4	2.53	1.7e-02
Trichlorophenol, 2,4,6-	88062	197.5	3.69	5.0e-02
Tris(2,3-dibromopropyl)phosphate	126727	697.6	4.98	3.6e-04

Table 5-7. (continued)

Chemical	CAS No.	MWT	log K_{ow}	K_p (cm/hr)
Tris(aziridinyl)-para-benzoquinone	68768	231.3	-1.34	8.3e-06
Urea	57136	60.0	-2.11	2.6e-05
Vinyl bromide	593602	107.0	1.57	5.5e-03
Vinyl chloride	75014	62.5	1.36	7.3e-03
Water	7732185	18.0	-1.38	1.6e-04
Xylene, m-	108383	106.2	3.20	8.0e-02

5.3. ESTIMATING THE DERMALLY ABSORBED DOSE PER EVENT

As discussed in Chapter 4 the new nonsteady-state approach for estimating the dermally absorbed dose from water appears to offer significant advantages (over the traditional steady-state approach) for risk assessment application. First, the method more accurately reflects normal human exposure conditions since the short contact times associated with bathing and swimming generally mean that steady state will not occur. Second, the method accounts for the dose that can occur after the actual exposure event due to absorption of contaminants stored in skin lipids. For these reasons, it is recommended as the preferred approach. However, the nonsteady-state approach was developed for application to organics which exhibit octanol-water partitioning. Thus, it is not applicable to inorganics. Hopefully, nonsteady-state procedures applicable to inorganics can be developed in the future. Meanwhile, it is recommended that the traditional steady-state approach be applied to inorganics. As discussed below, use of the nonsteady-state model for organics has implications for how to select K_p values for these chemicals.

The nonsteady-state model requires input parameters which are difficult to measure such as the stratum corneum diffusion coefficient (D_{sc}). Thus, these chemical specific factors must generally be estimated. Cleek and Bunge (1991) derived a procedure to estimate D_{sc} (as presented in Chapter 4) using the Potts and Guy correlation for estimating K_p values. Therefore for purposes of internal consistency, the K_p value used in the nonsteady-state model should also be the K_p derived from the

Potts and Guy correlation. This leads to the somewhat unexpected recommendation that for organics, K_p values predicted by the correlation should be used instead of the measured values derived from experiments. As discussed in Section 5.1 experimental K_p data were found for about 70 chemicals of potential environmental interest. These data were reviewed and K_p's selected and scored to indicate their reliability for representing human exposure conditions (as summarized in Table 5-3). As shown in Table 5-8, the experimentally derived K_p's agree reasonably well with the K_p's predicted from the correlation. The differences between the measured and predicted K_p's differ by more than a factor of 5 for only 16 of the 70 chemicals tested. Of these 16 chemicals where significant discrepancies were noted, 10 involved experiments using nonhuman species or the disappearance technique which is widely regarded as inaccurate. The remaining 6 chemicals were tested using in vitro experiments with human skin. This procedure is considered most reliable and all the data used to derive the Potts and Guy correlation were based on this procedure. Thus, the discrepancies between the predicted and measured K_p's for these 6 chemicals are difficult to explain. Standard experimental protocol for these studies do not exist and experimental, analytical, and quality control procedures differ widely among individual laboratories. An advantage of using the K_p's as predicted from the correlation is that it tends to smooth out such differences between laboratories and any experimental error. As new experimental data comes available, it can be used to refine the Potts and Guy correlation and hopefully reduce such discrepancies.

Based on the conclusions and recommendations presented earlier in this Chapter and in Chapter 4, the following procedures were derived for estimating DA_{event}. DA_{event}, as used in this context, represents the absorbed dose per cm^2 of exposed skin occurring during a single water contact event such as bathing or swimming. Information about water contact event times (t_{event}) is presented in Chapter 8.

5.3.1. Estimating DA_{event} for Inorganics

STEP 1. Get K_p from Table 5-3, for other inorganics use the following default assumption:

$$\textit{For Inorganics:}\quad K_p^w = 10^{-3}\ cm/hr\ (\textit{default value}) \qquad (5.9)$$

STEP 2. Evaluate DA_{event} using steady-state approach:

$$DA_{event} = K_p^w\, C_w\, t_{event} \qquad (5.10)$$

where:

DA_{event} = Dose absorbed per unit area per event (mg/cm^2-event)
K_p^w = Permeability coefficient from water (cm/hr)
C_w = Concentration of chemical in water (mg/cm^3)
t_{event} = duration of event (hr/event)

5.3.2 Estimating DA_{event} for Organics

STEP 1. Get K_p (cm/hour) from Table 5-7, for other organics estimate as follows:

$$\textit{For Organics:}\quad Log\ K_p = -\ 2.72 + 0.71\ \log K_{o/w} - 0.0061\ MW \qquad (5.11)$$

STEP 2. Calculate B (dimensionless):

$$\textit{For organics:}\quad B = \frac{K_{o/w}}{10^4} \qquad (5.12)$$

For organics, log $K_{o/w}$ of over 200 common contaminants are listed in Table 5-7. For those not available in Table 5-7, log $K_{o/w}$ can be found in several databases or handbooks (Hansch and Leo, 1979).

STEP 3. Calculate D_{sc} (cm^2/hour) from the following equation, assuming that l_{sc} = 10 μm = 10^{-3} cm (this equation was derived from Equation (5.8), assuming that Log $K_{sc/w}$ was given by Equation [4.48]):

$$Log \frac{D_{sc}}{l_{sc}} = -2.72 - 0.0061\ MW \tag{5.13}$$

STEP 4. Calculate τ (hour) from the following equation, assuming that l_{sc} = 10 μm = 10^{-3} cm,

$$\tau = \frac{l_{sc}^2}{6\ D_{sc}} \tag{5.14}$$

STEP 5. Calculate t^* (hour), based on the value of B:

$$If\ B \leq 0.1,\ then\ t^* = 2.4\ \tau \tag{5.15}$$

$$If\ 0.1 \leq B \leq 1.17,\ then\ t^* = (8.4 + 6 \log B)\ \tau \tag{5.16}$$

$$If\ B \geq 1.17,\ then\ t^* = 6\ (b - \sqrt{b^2 - c^2}\ )\ \tau \tag{5.17}$$

where:

$$b = \frac{2}{\pi} (1 + B)^2 - c \tag{5.18}$$

$$c = \frac{1 + 3\, B}{3} \tag{5.19}$$

STEP 6. Calculate DA_{event} (mg/cm^2-event):

$$If\ t_{event} < t^*,\ then:\ DA_{event} = 2\ K_p\ C_v \sqrt{\frac{6\ \tau\ t_{event}}{\pi}} \tag{5.20}$$

$$If\ t_{event} > t^*,\ then:\ DA_{event} = K_p\ C_v \left[\frac{t_{event}}{1 + B} + 2\ \tau \left(\frac{1 + 3\ B}{1 + B}\right)\right] \tag{5.21}$$

This full procedure is necessary only for compounds that have not been evaluated in this Chapter. Steps 1 through 5 in the above procedure have already been conducted for the compounds listed in this Chapter with recommended K_p values based on the predictions. For these compounds, τ and t* have been calculated and are reported in Table 5-8. These values were generated assuming that $l_{sc} = 10\ \mu m = 10^{-3}$ cm as a conservative estimate. Once the compound of interest has been located in Table 5-8, then the following procedure should be used: get B, K_p, τ, and t^* from Table 5-8 and calculate DA_{event} as in Step 6 above.

Exposure assessors are cautioned that this procedure for organics is based on a recently developed model which is currently being reviewed by the scientific community. On a conceptual basis, it has advantages over the traditional approach involving direct application of Fick's first law.

One, it accounts for the unsteady-state conditions that characterize the relatively short exposure periods associated with bathing. Two, it accounts for the dose that can occur after the actual exposure incident due to absorption of contaminants stored in the skin lipids. Actual calculations performed by EPA have shown that this approach provides a more conservative total absorbed dose over the traditional steady-state equation for organic compounds. Preliminary testing showed that this new approach indicates that the dermal dose resulting from 10-minute showers exceeds the dose associated with drinking 2 L/day for a number of the pollutants listed in Table 5-8. For the fastest penetrating chemicals the dermal dose was predicted to exceed the ingested dose by about two orders of magnitude (see Chapter 9 for further discussion of this comparison). This seems counterintuitive and raises concerns that the model may be overly conservative. Lack of data makes validation of the model very difficult. Further discussion on the practical considerations to make during dermal exposure assessments is offered in Chapter 10.

Table 5-8. K_p, τ, t^*, and B for Common Pollutants

Chemical	CAS No.	Measured Kp (cm/hr)	Estimated Kp (cm/hr)	τ (hr)	t^* (hr)	B
ORGANICS:						
Acetaldehyde	75070		7.2e-04	1.6e-01	3.9e-01	6.0e-05
Acetamide	60355		1.1e-04	2.0e-01	4.8e-01	5.5e-06
Acetylaminofluorene, 2-	53963		1.7e-02	2.0e+00	7.7e+00	1.7e-01
Acrolein	107028		7.4e-04	1.9e-01	4.6e-01	7.9e-05
Acrylamide	79061		2.4e-04	2.4e-01	5.7e-01	2.1e-05
Acrylonitrile	107131		1.4e-03	1.8e-01	4.4e-01	1.8e-04
Aldrin	309002		1.6e-03	1.5e+01	3.6e+01	1.0e-01
Allyl chloride	107051		7.0e-03	2.6e-01	6.2e-01	2.8e-03
Amino-2-methylanthraquinone, 1-	82280		6.6e-03	2.4e+00	5.9e+00	6.3e-02
Aminoanthraquinone, 2-	117793		2.8e-03	2.0e+00	4.8e+00	1.4e-02
Aminoazobenzene, p-	60093		8.7e-03	1.4e+00	3.3e+00	4.2e-02
Aminoazotoluene, o-	97563		4.9e-02	2.1e+00	1.6e+01	8.3e-01
Aminobiphenyl, 4-	92671		1.7e-02	9.4e-01	2.3e+00	6.3e-02
Aniline	62533	4.1e-02	2.2e-03	3.2e-01	7.8e-01	7.9e-04
Anisidine, o-	90040		1.7e-03	6.7e-01	1.6e+00	1.5e-03
Auramine	492808		1.5e-02	3.7e+00	2.1e+01	3.5e-01
Benzene	71432	1.1e-01	2.1e-02	2.6e-01	6.3e-01	1.3e-02
Benzidine	92875		1.3e-03	1.2e+00	2.8e+00	2.2e-03
Benzo-a-anthracene	56553		8.1e-01	2.2e+00	1.0e+01	4.6e+01

Table 5-8. (continued)

Chemical	CAS No.	Measured Kp (cm/hr)	Estimated Kp (cm/hr)	τ (hr)	t^* (hr)	B
Benzo-a-pyrene	50328		1.2e+00	2.9e+00	1.4e+01	1.3e+02
Benzo-b-fluoranthene	205992		1.2e+00	3.0e+00	1.4e+01	1.3e+02
Benzoic acid	65850		7.3e-03	4.9e-01	1.2e+00	7.4e-03
Benzotrichloride	98077		1.5e-02	1.4e+00	3.2e+00	8.3e-02
Benzyl chloride	100447		1.4e-02	5.2e-01	1.2e+00	2.0e-02
Bis(2-chloroethyl)ether	111444		2.1e-03	6.5e-01	1.6e+00	1.9e-03
Bromodichloromethane	75274		5.8e-03	8.7e-01	2.1e+00	1.2e-02
Bromoform	75252		2.6e-03	3.0e+00	7.3e+00	2.3e-02
Bromomethane	74839		3.5e-03	3.3e-01	8.0e-01	1.5e-03
Bromophenol, p-	106412	3.6e-02	1.3e-02	9.9e-01	2.4e+00	4.5e-02
Butadiene, 1,3-	106990		2.3e-02	1.9e-01	4.5e-01	9.8e-03
Butanediol, 2,3-	513859	5.0e-05	1.2e-04	3.1e-01	7.4e-01	1.2e-05
Butanol, n-	71363	2.5e-03	1.9e-03	2.5e-01	5.9e-01	4.5e-04
Butoxyethanol, 2-	111762	1.2e-02	1.4e-03	4.6e-01	1.1e+00	6.8e-04
Captan	133062		1.3e-03	5.9e+00	1.4e+01	2.2e-02
Carbon disulfide	75150	5.0e-01	2.4e-02	2.7e-01	6.5e-01	1.7e-02
Carbon tetrachloride	56235		2.2e-02	7.6e-01	1.8e+00	6.8e-02
Chlordane	57749		5.2e-02	2.8e+01	1.3e+02	3.5e+01

Table 5-8. (continued)

Chemical	CAS No.	Measured Kp (cm/hr)	Estimated Kp (cm/hr)	τ (hr)	t^* (hr)	B
Chlordane (cis)	5103719		4.6e-02	2.8e+01	1.3e+02	3.0e+01
Chlordane (trans)	5103742		4.6e-02	2.8e+01	1.3e+02	3.0e+01
Chlorobenzene	108907		4.1e-02	4.3e-01	1.0e+00	6.9e-02
Chlorocresol	59507	5.0e-02	4.1e-02	6.5e-01	1.9e+00	1.3e-01
Chlorodibromomethane	124481		3.9e-03	1.6e+00	3.9e+00	1.7e-02
Chloroethane	75003		8.0e-03	2.2e-01	5.2e-01	2.7e-03
Chloroform	67663	1.3e-01	8.9e-03	4.7e-01	1.1e+00	9.3e-03
Chloromethane	74873		4.2e-03	1.8e-01	4.3e-01	8.1e-04
Chlorophenol, o-	95578	3.3e-02	1.1e-02	5.3e-01	1.3e+00	1.4e-02
Chlorophenol, p-	106489	3.6e-02	1.6e-02	5.3e-01	1.3e+00	2.5e-02
Chlorothalonil	1897456		2.5e-02	3.7e+00	2.8e+01	7.2e-01
Chloroxylenol		6.0e-02	3.0e-04	5.6e-01	1.3e+00	1.0e-04
Chrysene	218019		8.1e-01	2.2e+00	1.0e+01	4.6e+01
Cresidine, p-	120718		4.3e-03	6.0e-01	1.4e+00	4.7e-03
Cresol, m-	108394	1.5e-02	1.0e-02	4.0e-01	9.6e-01	9.1e-03
Cresol, o-	95487	1.6e-02	1.0e-02	4.0e-01	9.6e-01	8.9e-03
Cresol, p-	106445	1.8e-02	1.0e-02	4.0e-01	9.6e-01	8.7e-03
DDD	72548		2.8e-01	7.8e+00	3.7e+01	6.3e+01

Table 5-8. (continued)

Chemical	CAS No.	Measured Kp (cm/hr)	Estimated Kp (cm/hr)	τ (hr)	t^* (hr)	B
DDE	72559		2.4e-01	7.6e+00	3.6e+01	4.9e+01
DDT	50293		4.3e-01	1.3e+01	6.0e+01	2.3e+02
Decanol	112301	8.0e-02	1.7e-01	8.1e-01	5.6e+00	1.3e+00
Di-2-ethylhexyl phthalate	117817		3.3e-02	2.1e+01	1.0e+02	1.3e+01
Diaminoanisole, 2,4-	615054		2.3e-04	6.1e-01	1.5e+00	7.6e-05
Diaminotoluene	95807		6.0e-04	4.9e-01	1.2e+00	2.2e-04
Diaminotoluene, 2,4-	101804		3.3e-03	1.5e+00	3.5e+00	1.1e-02
Dibenzo(a,h)anthracene	53703		2.7e+00	4.4e+00	2.1e+01	6.9e+02
Dibutyl phthalate	84742		3.3e-02	4.3e+00	2.9e+01	1.3e+00
Dichlorobenzene, 1,2-	95501		6.1e-02	6.9e-01	3.2e+00	2.4e-01
Dichlorobenzene, 1,3-	541731		8.7e-02	6.9e-01	4.1e+00	4.0e-01
Dichlorobenzene, 1,4-	106467		6.2e-02	6.9e-01	3.3e+00	2.5e-01
Dichlorobenzidine, 3,3'	91941		1.7e-02	3.1e+00	1.7e+01	3.2e-01
Dichlorodifluoromethane	75718		1.2e-02	4.8e-01	1.1e+00	1.4e-02
Dichloroethane, 1,1-	75343		8.9e-03	3.5e-01	8.4e-01	6.2e-03
Dichloroethane, 1,2-	107062		5.3e-03	3.5e-01	8.4e-01	3.0e-03
Dichloroethylene, 1,1-	75354		1.6e-02	3.4e-01	8.2e-01	1.3e-02
Dichloroethylene, 1,2- (trans)	540590		1.0e-02	3.4e-01	8.2e-01	7.2e-03

Table 5-8. (continued)

Chemical	CAS No.	Measured Kp (cm/hr)	Estimated Kp (cm/hr)	τ (hr)	t^* (hr)	B
Dichlorophenol, 2,4-	120832	6.0e-02	2.3e-02	8.6e-01	2.1e+00	8.3e-02
Dichloropropane, 1,2-	78875		1.0e-02	4.3e-01	1.0e+00	1.0e-02
Dichloropropene, 1,3-	542756		5.5e-03	4.2e-01	1.0e+00	4.0e-03
Dichlorvos	62737		9.5e-04	1.9e+00	4.7e+00	3.0e-03
Dieldrin	60571		1.6e-02	1.8e+01	9.4e+01	3.6e+00
Diepoxybutane	1464535		2.8e-05	2.9e-01	7.0e-01	1.4e-06
Diethyl phthalate	84662		4.8e-03	2.0e+00	4.7e+00	3.0e-02
Diethyl sulfate	64675		1.4e-03	7.6e-01	1.8e+00	1.4e-03
Dimethoxybenzidine, 3,3'-	119904		1.0e-03	3.1e+00	7.5e+00	6.5e-03
Dimethyl phthalate	131113		1.6e-03	1.3e+00	3.2e+00	3.6e-03
Dimethyl sulfate	77781		2.2e-03	5.1e-01	1.2e+00	1.4e-03
Dimethylamine, n-nitroso-	62759		2.7e-04	2.5e-01	5.9e-01	2.7e-05
Dimethylaminoazobenzene, 4-	60117		1.4e-01	2.1e+00	1.0e+01	3.8e+00
Dimethylbenzidine, 3,3'-	119937		4.4e-03	1.7e+00	4.1e+00	2.2e-02
Dimethylcarbamyl chloride	79447		4.2e-04	4.0e-01	9.5e-01	1.0e-04
Dimethylhydrazine, 1,1-	57147		7.1e-05	2.0e-01	4.9e-01	3.2e-06
Dimethylphenol, 2,4-	105679	1.1e-01	1.5e-02	4.9e-01	1.2e+00	2.0e-02
Dimethylphenol, 3,4-	95658	4.0e-02	1.3e-02	4.9e-01	1.2e+00	1.7e-02

Table 5-8. (continued)

Chemical	CAS No.	Measured Kp (cm/hr)	Estimated Kp (cm/hr)	τ (hr)	t^* (hr)	B
Dinitrophenol, 2,4-	51285	3.2e-03	1.8e-03	1.2e+00	2.8e+00	3.5e-03
Dinitrotoluene, 2,4-	121142		3.8e-03	1.1e+00	2.7e+00	9.5e-03
Dinitrotoluene, 2,6-	606202		2.5e-03	1.1e+00	2.7e+00	5.2e-03
Dioxane, 1,4-	123911	4.0e-04	3.6e-04	3.0e-01	7.2e-01	5.4e-05
Diphenylamine, n-nitroso-	86306		2.0e-02	1.4e+00	4.5e+00	1.3e-01
Diphenylhydrazine, 1,2-	122667		1.8e-02	1.2e+00	2.8e+00	8.7e-02
Dipropylamine, n-nitroso-	621647		2.8e-03	5.4e-01	1.3e+00	2.3e-03
Endrin	72208		1.6e-02	1.8e+01	9.4e+01	3.6e+00
Epichlorohydrin	106898		3.7e-04	3.2e-01	7.6e-01	6.2e-05
Ethanol	64175	8.0e-04	6.0e-04	1.7e-01	4.0e-01	4.9e-05
Ethanol, 2-(2-butoxyethoxy)-	112345		4.4e-05	8.5e-01	2.0e+00	1.2e-05
Ethanol, 2-(2-ethoxyethoxy)-	111900		2.5e-04	5.7e-01	1.4e+00	8.3e-05
Ethanol, 2-(2-methoxyethoxy)-	111773		1.8e-04	4.7e-01	1.1e+00	3.8e-05
Ethoxyethanol, 2-	110805	3.0e-04	4.6e-04	3.1e-01	7.4e-01	7.9e-05
Ethoxyethyl acetate, 2-	111159		8.6e-04	5.6e-01	1.3e+00	4.5e-04
Ethyl acrylate	140885		4.0e-03	3.6e-01	8.6e-01	2.1e-03
Ethyl carbamate	51796		4.3e-04	3.1e-01	7.3e-01	7.1e-05
Ethyl ether	60297	1.7e-02	2.9e-03	2.5e-01	5.9e-01	7.8e-04
Ethylbenzene	100414	1.0e+00	7.4e-02	3.9e-01	1.3e+00	1.4e-01

Table 5-8. (continued)

Chemical	CAS No.	Measured Kp (cm/hr)	Estimated Kp (cm/hr)	τ (hr)	t^* (hr)	B
Ethylene oxide	75218		6.3e-04	1.6e-01	3.9e-01	5.0e-05
Ethylenedibromide	106934		3.3e-03	1.2e+00	2.9e+00	9.1e-03
Ethyleneimine	151564		1.7e-04	1.6e-01	3.8e-01	7.6e-06
Ethylenethiourea	96457		1.7e-04	3.4e-01	8.1e-01	2.2e-05
Ethylphenol, p-	123079	3.5e-02	1.4e-02	4.7e-01	1.1e+00	1.8e-02
Fluoranthene	206440		3.6e-01	1.5e+00	7.3e+00	8.9e+00
Formaldehyde	50000		2.2e-03	1.3e-01	3.2e-01	2.2e-04
Glycerol	56815	1.4e-04	2.9e-05	3.2e-01	7.7e-01	1.7e-06
Heptachlor	76448		1.1e-02	1.7e+01	9.4e+01	1.9e+00
Heptanol	111706	3.8e-02	1.9e-02	4.5e-01	1.1e+00	2.6e-02
Hexachlorobenzene	118741		2.1e-01	4.8e+00	2.3e+01	2.0e+01
Hexachlorobutadiene	87683		1.2e-01	3.4e+00	1.7e+01	6.0e+00
Hexachloroethane	67721		4.2e-02	2.4e+00	1.9e+01	8.5e-01
Hexamethylphosphoramide	680319		1.6e-04	1.1e+00	2.6e+00	1.1e-04
Hexanol	111273	3.0e-02	1.3e-02	3.7e-01	8.8e-01	1.1e-02
Hydrazine/Hydrazine sulfate	302012		4.1e-05	1.4e-01	3.3e-01	8.5e-07
Indeno(1,2,3-CD)pyrene	193395		1.9e+00	4.2e+00	2.0e+01	3.8e+02
Isophorone	78591		4.2e-03	6.1e-01	1.5e+00	4.7e-03
Lindane	58899		1.4e-02	5.2e+00	3.5e+01	5.2e-01

Table 5-8. (continued)

Chemical	CAS No.	Measured Kp (cm/hr)	Estimated Kp (cm/hr)	τ (hr)	t^* (hr)	B
Mechlorethamine	51752		1.2e-03	7.8e-01	1.9e+00	1.2e-03
Methanol	67561	1.6e-03	3.5e-04	1.4e-01	3.3e-01	1.7e-05
Methoxyethanol, 2-	109864		1.9e-04	2.5e-01	6.1e-01	1.7e-05
Methoxypropan-2-ol, 1-	107982		4.0e-04	3.1e-01	7.4e-01	6.6e-05
Methyl ethyl ketone	78933	5.0e-03	1.1e-03	2.4e-01	5.8e-01	1.9e-04
Methyl hydroxybenzoate	99763	9.1e-03	5.2e-03	7.4e-01	1.8e+00	8.3e-03
Methyl iodide	74884		3.1e-03	6.4e-01	1.5e+00	3.2e-03
Methylaziridine, 2-	75558		3.2e-04	1.9e-01	4.7e-01	2.5e-05
Methylene bis(2-chloroaniline), 4,4'-	101144		2.8e-02	3.7e+00	3.0e+01	8.7e-01
Methylene bis(N,N'-dimethyl)aniline, 4,4'-	101611		1.3e-01	3.1e+00	1.5e+01	5.6e+00
Methylene chloride	75092		4.5e-03	2.9e-01	6.9e-01	1.8e-03
Methylenedianiline, 4,4'-	101779		1.6e-03	1.4e+00	3.4e+00	3.9e-03
Michler's ketone	90948		3.4e-02	3.8e+00	ERR	1.2e+00
Mustard Gas	505602		5.6e-03	8.2e-01	2.0e+00	1.1e-02
Naphthalene	91203		6.9e-02	5.3e-01	2.2e+00	2.0e-01
Naphthol, b-	135193	2.8e-02	2.6e-02	6.6e-01	1.6e+00	6.9e-02
Naphthylamine, 1-	134327		1.0e-02	6.5e-01	1.6e+00	1.8e-02
Naphthylamine, 2-	91598		1.1e-02	6.5e-01	1.6e+00	1.9e-02

Table 5-8. (continued)

Chemical	CAS No.	Measured Kp (cm/hr)	Estimated Kp (cm/hr)	τ (hr)	t^* (hr)	B
Nitrilotriacetic acid	139139		9.7e-05	1.3e+00	3.1e+00	6.6e-05
Nitro-o-anisidine, 5-	99592		2.5e-03	7.5e-01	1.8e+00	2.9e-03
Nitrobiphenyl, 4-	92933		5.5e-02	1.4e+00	1.0e+01	5.9e-01
Nitrofen	1836755		3.0e-01	4.7e+00	2.2e+01	3.4e+01
Nitrophenol, 2-	88755	1.0e-01	5.0e-03	6.2e-01	1.5e+00	6.2e-03
Nitrophenol, 2-amino-4-	99570	7.0e-04	2.0e-03	7.6e-01	1.8e+00	2.3e-03
Nitrophenol, 3-	554847	5.6e-03	7.1e-03	6.2e-01	1.5e+00	1.0e-02
Nitrophenol, 4-	100027	5.6e-03	6.1e-03	6.2e-01	1.5e+00	8.1e-03
Nitrophenol, 4-amino-2-	119346	3.0e-03	1.1e-03	7.6e-01	1.8e+00	9.1e-04
Nitropropane, 2-	79469		1.0e-03	4.1e-01	9.8e-01	3.6e-04
Nitroso-di-n-butylamine, n-	924163		4.8e-03	8.1e-01	1.9e+00	8.3e-03
Nitroso-N-ethylurea, n-	759739		5.4e-04	4.5e-01	1.1e+00	1.7e-04
Nitroso-N-methylurea, n-	684935		4.3e-04	3.7e-01	8.9e-01	9.3e-05
Nitrosodiethanolamine, n-	1116547	5.0e-06	2.2e-05	5.7e-01	1.4e+00	2.6e-06
Nitrosodiethylamine, n-	55185		1.2e-03	3.0e-01	7.2e-01	3.0e-04
Nitrosodiphenylamine, p-	156105		3.6e-02	1.4e+00	7.6e+00	3.2e-01
Nitrosomethylvinylamine, n-	4549400		5.7e-04	2.9e-01	7.0e-01	9.9e-05
Nitrosomorpholine, n-	59892		1.8e-04	4.5e-01	1.1e+00	3.6e-05

Table 5-8. (continued)

Chemical	CAS No.	Measured Kp (cm/hr)	Estimated Kp (cm/hr)	τ (hr)	t^* (hr)	B
Nitrosonornicotine, n-	16543558		1.7e-04	1.1e+00	2.5e+00	1.1e-04
Nitrosopiperidine, n-	100754		2.5e-05	1.2e+01	2.9e+01	2.3e-04
Nonanol	143088	6.0e-02	7.3e-02	6.6e-01	3.4e+00	2.9e-01
Octanol	111875	6.1e-02	3.9e-02	5.4e-01	1.3e+00	9.3e-02
Parathion	56382		1.7e-02	5.2e+00	3.8e+01	6.8e-01
PCB-chlorobiphenyl, 4-	2051629		1.3e+00	5.3e+00	2.5e+01	3.2e+02
PCB-hexachlorobiphenyl	26601649		7.1e-01	1.4e+01	6.6e+01	5.2e+02
Pentachloronitrobenzene	82688		5.9e-02	5.5e+00	2.8e+01	4.4e+00
Pentachlorophenol	87865		6.5e-01	3.7e+00	1.7e+01	7.2e+01
Pentanol	71410	6.0e-03	7.1e-03	3.0e-01	7.2e-01	3.6e-03
Pentanone, 4-methyl-2-	108101		3.3e-03	3.6e-01	8.6e-01	1.5e-03
Phenanthrene	85018		2.3e-01	1.1e+00	5.6e+00	2.9e+00
Phenol	108952	8.2e-03	5.5e-03	3.3e-01	7.9e-01	2.9e-03
Phenol, 4,6-dinitro-2-methyl-	534521		3.8e-03	1.4e+00	3.4e+00	1.3e-02
Propanol	71238	1.7e-03	1.3e-03	2.0e-01	4.9e-01	2.0e-04
Propiolactone, beta-	57578		3.3e-04	2.4e-01	5.8e-01	3.5e-05
Propylene oxide	75569		8.9e-04	2.0e-01	4.7e-01	1.1e-04
Resorcinol	108463	2.4e-04	1.5e-03	4.1e-01	9.9e-01	6.3e-04
Safrole	94597		1.5e-02	8.5e-01	2.0e+00	4.6e-02

Table 5-8. (continued)

Chemical	CAS No.	Measured Kp (cm/hr)	Estimated Kp (cm/hr)	τ (hr)	t^* (hr)	B
Styrene	100425	6.7e-01	5.5e-02	3.8e-01	9.1e-01	8.9e-02
Styrene oxide	96093		4.9e-03	4.7e-01	1.1e+00	4.1e-03
TCDD	1746016		1.4e+00	8.1e+00	3.8e+01	6.3e+02
Tetrachlorethylene	127184	3.7e-01	4.8e-02	9.0e-01	4.3e+00	2.5e-01
Tetrachloroethane, 1,1,2,2-	79345		9.0e-03	9.2e-01	2.2e+00	2.5e-02
Thioacetamide	62555		2.1e-03	2.5e-01	6.0e-01	5.1e-04
Thiodianiline, 4,4'-	139651		2.5e-03	1.8e+00	4.4e+00	1.1e-02
Thiourea	62566	9.6e-05	1.4e-04	2.5e-01	6.1e-01	1.1e-05
Thymol	89838	5.3e-02	5.1e-02	7.2e-01	3.0e+00	2.0e-01
Toluene	108883	1.0e+00	4.5e-02	3.2e-01	7.7e-01	5.4e-02
Toluidine hydrochloride, o-	636215		2.1e-03	6.5e-01	1.6e+00	1.9e-03
Toluidine, o-	95534		3.7e-03	3.9e-01	9.4e-01	2.1e-03
Toxaphene	8001352		1.5e-02	2.9e+01	1.4e+02	6.6e+00
Trichlorobenzene, 1,2,4-	120821		1.0e-01	1.1e+00	9.3e+00	9.5e-01
Trichloroethane, 1,1,1-	71556		1.7e-02	5.7e-01	1.4e+00	3.1e-02
Trichloroethane, 1,1,2-	79005		8.4e-03	5.7e-01	1.4e+00	1.1e-02
Trichloroethylene	79016	2.3e-01	1.6e-02	5.5e-01	1.3e+00	2.6e-02
Trichlorofluoromethane	75694		1.7e-02	6.0e-01	1.4e+00	3.4e-02

Table 5-8. (continued)

Chemical	CAS No.	Measured Kp (cm/hr)	Estimated Kp (cm/hr)	τ (hr)	t^* (hr)	B
Trichlorophenol, 2,4,6-	88062	5.9e-02	5.0e-02	1.4e+00	9.2e+00	4.9e-01
Tris(2,3-dibromopropyl)phosphate	126727		3.6e-04	1.6e+03	7.6e+03	9.5e+00
Tris(aziridinyl)-para-benzoquinone	68768		8.3e-06	2.3e+00	5.4e+00	4.6e-06
Urea	57136	1.2e-04	2.6e-05	2.0e-01	4.9e-01	7.8e-07
Vinyl bromide	593602		5.5e-03	3.9e-01	9.4e-01	3.7e-03
Vinyl chloride	75014		7.3e-03	2.1e-01	5.1e-01	2.3e-03
Water	7732185	1.5e-03	1.6e-04	1.1e-01	2.7e-01	4.2e-06
Xylene, m-	108383		8.0e-02	3.9e-01	1.4e+00	1.6e-01

SECTION 5 APPENDIX: SUMMARY OF COMPOUND-SPECIFIC K_p DATA

2-Amino-4-nitrophenol

Using information presented in Bronaugh (1982), Bronaugh and Congdon (1984) reported a K_p value for 2-amino-4-nitrophenol of 6.6×10^{-4} cm/hour. This value was based on in vitro testing using an aqueous vehicle applied to abdominal human epidermal tissue maintained at 32°C. Human abdominal skin obtained at autopsy was used, but the metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = $(10 + 0 + 4 + 0) \times 5 = 70$.

4-Amino-2-nitrophenol

Bronaugh and Congdon (1984) reported a K_p value for 4-amino-2-nitrophenol of 2.8×10^{-3} cm/hour. This value was based on in vitro testing using an aqueous vehicle applied to abdominal human epidermal tissue maintained at 32°C. Human abdominal skin obtained at autopsy was used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = $(10 + 0 + 4 + 0) \times 5 = 70$.

Aniline

No studies reported K_p data for this chemical, however, flux of aniline from aqueous media was reported by Baranowska-Dutkiewicz (1982). The average absorption rates for aniline across human skin exposed in vivo (immersion of hands) to a 2% aqueous solution of aniline for 60 minutes was reported to be 0.82 mg/cm^2/hour. The amount of aniline absorbed was calculated based on the amount of p-aminophenol excreted in the urine over the 24-hour period following exposure. A K_p of 0.041 cm/hour can be calculated by dividing the flux value by the concentration of aniline in aqueous solution, 20 mg/cm^3. This study provides a very useful K_p for water-contact scenarios, because the data were obtained in humans in vivo for aniline in dilute aqueous solutions. The absorption rate at the longer exposure, 60 minutes, was selected over that measured at 30 minutes to ensure that conditions closer to a steady-state rate of absorption were occurring. The absorption rate from the 2% solution was chosen because it is higher than the 1% solution also tested.

In addition to the flux values obtained for aniline in aqueous solution, Baranowska-Dutkiewicz (1982) obtained flux values for liquid aniline and also reported flux values for liquid aniline from other researchers. Although these values for neat exposures are similar to those obtained for aqueous solutions of aniline, they are not as relevant for the water-contact exposure scenarios. The flux value reported by Tsuruta (1986) is the one cited by Baranowska-Dutkiewicz (1982) and Piotrowski (1957) for liquid aniline.

The flux obtained by Baranowska-Dutkiewicz (1982) may underpredict the flux expected in the bathing scenario, because the temperature of the aqueous solutions was only about 20°C, and the body part exposed to the solution was only the hand, which has a stratum corneum that is significantly thicker than other tissues. The amount of aniline absorbed was a body burden measurement, calculated on the basis of the amount of p-aminophenol excreted in the urine during the 24-hour period from the beginning of the 60-minute exposure. Steady-state conditions were not verified. Weight-of-evidence scoring: species - 10, procedure - 1, PBPK model - 0, and steady-state - 0. Score = (10 + 1 + 0 + 0) x 5 = 55.

Benzene

Four studies reported K_p data for this chemical. The data reported by Blank and McAuliffe (1985) was selected as the most appropriate K_p value to estimate absorbed dose in the scenarios. These investigators reported a K_p of 0.111 cm/hour for the penetration of an aqueous solution of benzene through human abdominal skin in vitro. One other study, that of Dutkiewicz and Tyras (1968) as cited by Baranowska-Dutkiewicz (1982), also reported an absorption rate constant for benzene in aqueous solution, but no information was reported on the experimental conditions.

Other values from the Blank and McAuliffe (1985) paper were for the penetration of benzene through skin from various organic solvents, and are therefore inappropriate for water-contact data were obtained in humans in vivo for aniline in dilute aqueous solutions. The absorption rate at the longer exposure, 60 minutes, was selected over that measured at 30 minutes to ensure that conditions closer to a steady-state rate of absorption were occurring. The absorption rate from the 2% solution was chosen because it is higher than the 1% solution also tested.

In addition to the flux values obtained for aniline in aqueous solution, Baranowska-Dutkiewicz (1982) obtained flux values for liquid aniline and also reported flux values for liquid aniline from other researchers. Although these values for neat exposures are similar to those obtained for aqueous solutions of aniline, they are not as relevant for the water-contact exposure scenarios. The flux value reported by Tsuruta (1986) is the one cited by Baranowska-Dutkiewicz (1982) and Piotrowski (1957) for liquid aniline.

The flux obtained by Baranowska-Dutkiewicz (1982) may underpredict the flux expected in the bathing scenario, because the temperature of the aqueous solutions was only about 20°C, and the body part exposed to the solution was only the hand, which has a stratum corneum that is significantly thicker than other tissues. The amount of aniline absorbed was a body burden measurement, calculated on the basis of the amount of p-aminophenol excreted in the urine during the 24-hour period from the beginning of the 60-minute exposure. Steady-state conditions were not verified. Weight-of-evidence scoring: species - 10, procedure - 1, PBPK model - 0, and steady-state - 0. Score = $(10 + 1 + 0 + 0) \times 5 = 55$.

Benzene

Four studies reported K_p data for this chemical. The data reported by Blank and McAuliffe (1985) was selected as the most appropriate K_p value to estimate absorbed dose in the scenarios. These investigators reported a K_p of 0.111 cm/hour for the penetration of an aqueous solution of benzene through human abdominal skin in vitro. One other study, that of Dutkiewicz and Tyras (1968) as cited by Baranowska-Dutkiewicz (1982), also reported an absorption rate constant for benzene in aqueous solution, but no information was reported on the experimental conditions.

Other values from the Blank and McAuliffe (1985) paper were for the penetration of benzene through skin from various organic solvents, and are therefore inappropriate for water-contact scenarios. The other values reported are either for liquid benzene (Tsuruta, 1982; 1986) or benzene in the vapor phase (McDougal et al., 1987, 1990).

Human abdominal skin obtained at autopsy was used in the study by Blank and McAuliffe (1985). The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

p-Bromophenol

A single K_p value has been reported for this compound. Roberts et al. (1977) used human abdominal epidermal membranes and a number of aqueous concentrations of *p*-bromophenol in vitro to determine a K_p of 6.02×10^{-4} cm/minute (= 3.61×10^{-2} cm/hour). The stirred receptor cell contained distilled water. The temperature of the system was maintained at 25°C. A number of different concentrations of 2,4-dichlorophenol in aqueous solution were used in a series of such experiments to determine the K_p value. Epidermal membranes, separated from human abdominal skin, were obtained at autopsy and used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

2,3-Butanediol

Only one K_p has been reported in the literature for this compound. Blank et al. (1967) reported the K_p value as $< 0.05 \times 10^{-3}$ cm/hour for 2,3-butanediol in aqueous solution applied to human abdominal skin in vitro. The sensitivity of the assay presumably prevents a more quantitative characterization of the K_p. Therefore, 5×10^{-5} cm/hour was selected as an upper-bound estimate of the K_p for this compound. Human abdominal skin obtained at autopsy was used, but the metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

Butanol

K_p data for butanol are available in eight references (Del Terzo et al., 1986; Behl et al., 1983a,b, 1984; Garcia et al., 1980; Scheuplein and Blank, 1971, 1973; Blank et al., 1967). Values reported by Scheuplein and Blank (1971) and by Del Terzo and co-workers (1986) were from other studies. Blank et al. (1967) and Scheuplein and Blank (1973) presented the only K_p data for butanol derived using human skin. Unfortunately, Blank et al. (1967) provided only a range of values for the permeability coefficient. Therefore, the recommended K_p is from Scheuplein and Blank (1973), who reported a K_p of 2.5×10^{-3} cm/hour for abdominal epidermis in vitro at 25°C using an aqueous butanol solution (0.1 M) and a distilled water receptor. Human abdominal skin obtained at autopsy was used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = $(10 + 0 + 4 + 0) \times 5 = 70$.

2-Butanone (Methyl ethyl ketone)

Only one study has been identified that reported a K_p value for 2-butanone (Blank et al., 1967). This study was conducted using human abdominal skin in vitro and an aqueous vehicle, therefore, the values are especially applicable to water-contact scenarios. Blank et al. (1967) reported a K_p of 4 to 5×10^{-3} cm/hour for 2-butanone in an aqueous solution applied to the human abdominal skin in vitro. The upper-bound K_p value of 5×10^{-3} cm/hour is recommended for this compound. Human abdominal skin obtained at autopsy was used, but the metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = $(10 + 0 + 4 + 0) \times 5 = 70$.

2-Butoxyethanol

Flux values have been reported for neat 2-butoxyethanol applied in vivo to guinea pig skin (Johanson and Fernstrom, 1986, 1988) and to human skin (Johanson and Fernstrom, 1988), and to human skin (Dugard et al., 1984) in vitro. In addition, Johanson and Fernstrom (1988) tested five aqueous concentrations of this compound applied to guinea pig skin in vivo and reported flux values. The K_p calculated by Johanson and Fernstrom (1988) for the 5% (v/v) solution is 1.2×10^{-2} cm/hour. This is the only study available for the aqueous solution of this compound, so this is therefore the recommended K_p value. The study used female outbred guinea pigs and the amount of 2-butoxyethanol absorbed was quantified by a simple model, but not a physiologically based pharmacokinetic (PBPK) model. A steady-state condition was reached. Weight-of-evidence scoring: species - 4, procedure - 4, PBPK model - 0, and steady-state - 3. Score = (4 + 4 + 0 + 3) x 5 = 55.

2-(2-Butoxyethoxy)ethanol

The K_p for this compound has been reported in only one reference (Dugard et al., 1984). The value of this coefficient, 3.57×10^{-5} cm/hour, was generated using neat exposures to whole human abdominal skin, in vitro. The only K_p data available for this compound were obtained with the neat material; no K_p data were available for aqueous solutions, so the K_p data are not included in Table 5-3 and the weight-of-evidence scoring system has not been used to evaluate the K_p value(s).

Cadmium Compounds

Cadmium chloride has been tested by Skog and Wahlberg (1964) using an aqueous solution applied in vivo to guinea pigs, yielding a K_p estimate of 1.2×10^{-3} cm/hour. Wester et al. (1991) tested cadmium chloride in an aqueous vehicle applied to human skin in vitro, but insufficient information was provided to estimate a K_p. Therefore, the value of 1×10^{-3} cm/hour is recommended. Skog and Wahlberg (1964) used guinea pig skin in vivo and quantified the amount of cadmium chloride absorbed by disappearance measurements. Steady-state conditions were not verified. Weight-of-evidence scoring: species - 4, procedure - 1, PBPK model - 0, and steady-state - 0. Score = (4 + 1 + 0 + 0) x 5 = 25.

Carbon disulfide

The permeability of this compound has been tested in only one study. Baranowska-Dutkiewicz (1982) cited a previous study (Baranowska, 1968) that reported dermal absorption rate values for carbon disulfide (CS_2) in aqueous solutions applied to human skin at concentrations from 0.42 to 1.49 g/L were 0.23 to 0.79 mg/cm^2/hour. A K_p value of approximately 0.54 cm/hour is calculated from both the upper-bound and lower-bound flux estimates. Although this K_p was obtained using human skin and an aqueous solution of the compound, it should be used cautiously because little information is known about the conditions under which the study was conducted. A flux value of 9.7 mg/cm^2/hour for liquid CS_2 applied to human skin was also reported (Baranowska, 1968, as cited in Baranowska-Dutkiewicz, 1982), but was not selected because of the absence of an aqueous vehicle. Human skin was used in the aqueous in vivo study and although little information is available on this paper, it has been assumed that like other papers by Baranowska-Dutkiewicz, disappearance measurements were used to quantify the amount of carbon disulfide absorbed. Steady-state conditions were also probably not verified. Weight-of-evidence scoring: species - 10, procedure - 1, PBPK - 0, and steady-state - 0. Score = (10 + 1 + 0 + 0) x 5 = 55.

Chlorocresol

Huq et al. (1986) reported a K_p value for this compound of 1.19 x 10^{-1} cm/hour. The experiment used whole hairless mouse skin in an in vitro stirred cell system maintained at a temperature of 37°C. The receptor compartment contained a saline solution (pH = 6.2), while the donor compartment was loaded with an aqueous solution of 4-chloro-3-cresol (0.5 mg/mL, pH = 6.18). The estimated stratum corneum permeability was calculated to be 2.35 x 10^{-1} cm/hour, based on the whole skin experimental value.

In addition, Roberts et al. (1977), using human abdominal epidermal membranes in vitro, determined the K_p of an unspecified chlorocresol isomer to be 9.16 x 10^{-4} cm/min (= 5.5 x 10^{-2} cm/hour). A series of different concentrations of chlorocresol in aqueous solution were used. The stirred receptor cell contained distilled water. The temperature of the system was maintained at 25°C. (See *p*-Bromophenol for details of Roberts et al. [1977].) Because human tissues were used, the K_p of 5.5 x 10^{-2} cm/hour reported by Roberts et al. (1977) is the recommended value for chlorocresol. Epidermal membranes, separated from human abdominal skin, were obtained at autopsy and used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

Chloroform

Bogen et al. (1992) measured percutaneous absorption in hairless guinea pigs exposed for 70 minutes to a dilute aqueous solution of chloroform. An airtight glass chamber was used with no head space. Dermal uptake was estimated using a disappearance procedure consisting of comparing the rate of radiolabel loss from chamber water in systems with and without experimental animals. Radio label in urine and feces excreted after the experiment was measured and expressed as a fraction of the radio label lost from the chamber. The mean value of this fraction did not differ significantly from that obtained using animals injected with an equal dose of the compound. Thus, body burden measurements were used to confirm the accuracy of the disappearance procedure. On this basis, a weight-of-evidence score of 4 was deemed appropriate for the procedure. A K_p estimate of 0.13 cm/hour was estimated under steady-state conditions. Weight-of-evidence scoring: species - 4, procedure - 4, PBPK model - 0, and steady-state - 3. Score = (4 + 4 + 0 + 3) x 5 = 55.

2-Chlorophenol (*o*-chlorophenol)

Two papers reported K_p data for 2-chlorophenol, Huq et al. (1986) for hairless mouse skin and Roberts et al. (1977) for human skin. The recommended K_p value is therefore based on the data reported by Roberts et al. (1977). A series of in vitro experiments were performed using human abdominal epidermal membranes and a number of aqueous concentrations of *o*-chlorophenol to determine a K_p of 5.51 x 10^{-4} cm/minute (= 3.31 x 10^{-2} cm/hour). (See *p*-Bromophenol for details of Roberts et al. [1977].) Epidermal membranes, separated from human abdominal skin, were obtained at autopsy and used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

p-Chlorophenol

A single K_p value has been reported for this compound. Roberts et al. (1977) used human abdominal epidermal membranes and a number of aqueous concentrations of *p*-chlorophenol in vitro to determine a K_p of 6.05 x 10^{-4} cm/minute (= 3.63 x 10^{-2} cm/hour). (See *p*-Bromophenol for details of Roberts et al. [1977].) Epidermal membranes, separated from human abdominal skin, were obtained at autopsy and used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

Chloroxylenol (unspecified isomer)

Only a single K_p value has been identified for this compound. Roberts et al. (1977) performed a number of in vitro permeability experiments on human abdominal epidermal membranes with a series of different concentrations of chloroxylenol in an aqueous solution. The K_p was determined to be 9.84 x 10^{-4} cm/minute (= 5.90 x 10^{-2} cm/hour). (See *p*-Bromophenol for details of Roberts et al. [1977].) Epidermal membranes, separated from human abdominal skin, were obtained at autopsy and used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

Chromium Compounds

Sodium chromate has been tested by Wahlberg (1965b) using an aqueous solution applied to human skin in vitro, yielding a K_p estimate of 3.1 x 10^{-4} cm/hour. Somewhat higher results (estimated as about 2 x 10^{-3} cm/hour) were reported in guinea pig tests in vitro (Wahlberg, 1965b) and in vivo (Wahlberg and Skog, 1963; Wahlberg, 1970, 1971). Baranowska-Dutkiewicz (1981) conducted human in vivo tests with an aqueous vehicle, yielding similar values (K_p = 2.1 x 10^{-3} cm/hour). Thus, a value of 2 x 10^{-3} cm/hour is recommended. Both Baranowska-Dutkiewicz (1981) and Wahlberg (1971) use a disappearance technique to estimate flux values for this compound. (See

Chapter 3 for a discussion of the limitations of this technique.) The Baranowska-Dutkiewicz (1981) study was conducted on human forearm skin. The amount of sodium chromate absorbed was estimated by measuring the compound in the donor solution before and after exposure and determining the disappearance of the compound from the solution. The study did not verify steady-state conditions. Weight-of-evidence scoring: species - 10, procedure - 1, PBPK model - 0, and steady-state - 0. Score = (10 + 1 +0 + 0) x 5 = 55.

Sodium dichromate has been tested by Wahlberg (1968) using an aqueous solution applied to guinea pig skin in vivo, yielding a K_p estimate of $< 1.2 \times 10^{-3}$ cm/hour. A value of 1×10^{-3} cm/hour is recommended. The amount of sodium dichromate absorbed was quantified by disappearance measurements. Steady-state conditions were not verified. Weight-of-evidence scoring: species - 4, procedure - 1, PBPK model - 0, and steady-state - 0. Score = (4 + 1+ 0 + 0) x 5 = 25.

Chromium chloride has been tested by Wahlberg and Skog (1965) using an aqueous solution applied to guinea pig skin in vivo, yielding a K_p estimate of 1.4×10^{-3} cm/hour. A value of 1×10^{-3} cm/hour is recommended. The amount of chromium chloride absorbed was quantified by disappearance measurements. Steady-state conditions were not verified. Weight-of-evidence scoring: species - 4, procedure - 1, PBPK model - 0, and steady-state - 0 . Score = (4 + 1 + 0 + 0) x 5 = 25.

Cobalt Compounds

Wahlberg (1965b) tested cobalt chloride using an aqueous solution applied to human skin in vitro, yielding a K_p estimate of 4×10^{-4} cm/hour, and also obtained slightly lower results with guinea pig skin in vitro ($K_p = 1 \times 10^{-4}$ cm/hour). Wahlberg (1971) obtained somewhat higher results testing guinea pigs in vivo, $K_p = 1 \times 10^{-3}$ cm/hour. Wahlberg (1965b, 1971) used a "disappearance technique" to obtain the flux values reported in these papers. The uncertainties surrounding the use of data obtained by this technique are discussed in Chapter 3. This technique involves following the disappearance of a radiolabeled compound from the skin or from the test solution, rather than measuring the direct penetration of the compound across the skin. These uncertainties should be recognized when using these data to calculate the dermally absorbed dose of cobalt. A value of

4×10^{-4} cm/hour is recommended. Human abdominal skin obtained after autopsy was used. The metabolic capacity of the skin had not been maintained, but the applied dose of the chemical had been essentially infinite in concentration. There were continuous flow conditions in the receptor cell. Weight-of-evidence scoring: species - 10, continuous flow - 2, infinite dose - 4, and metabolism - 0. Score = (10 + 2 + 4 + 0) x 5 = 80.

m-Cresol

A single K_p value has been identified for this compound. Roberts et al. (1977) used human abdominal epidermal membranes and a number of aqueous concentrations of *m*-cresol, in vitro, to determine a K_p of 2.54×10^{-4} cm/minute (= 1.52×10^{-2} cm/hour). (See *p*-Bromophenol for details of Roberts et al. [1977].) Epidermal membranes, separated from human abdominal skin, were obtained at autopsy and used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

o-Cresol

A single K_p value has been identified for this compound. Roberts et al. (1977) used human abdominal epidermal membranes and a number of aqueous concentrations of *o*-cresol, in vitro, to determine a K_p of 2.62×10^{-4} cm/minute (= 1.57×10^{-2} cm/hour). (See *p*-Bromophenol for details of Roberts et al. [1977].) Epidermal membranes, separated from human abdominal skin, were obtained at autopsy and used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

p-Cresol

A single K_p value has been identified for this compound. Roberts et al. (1977) used human abdominal epidermal membranes and a number of aqueous concentrations of *p*-cresol, in vitro, to determine a K_p of 2.92 x 10^{-4} cm/minute (1.75 x 10^{-2} cm/hour). [See *p*-Bromophenol for details of Roberts et al. (1977).] Epidermal membranes, separated from human abdominal skin, were obtained at autopsy and used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

Decanol

Scheuplein and Blank (1973) provided the only available value for the K_p of decanol. In vitro experiments were conducted using human abdominal epidermis and an aqueous solution of decanol (3 x 10^{-4} M) at 25°C, yielding a K_p of 8.0 x 10^{-2} cm/hour. Human abdominal skin obtained at autopsy was used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

Dibutyl phthalate

Only one study was identified that reported K_p values for dibutyl phthalate (Scott et al., 1987). These investigators obtained K_p values for neat dibutyl phthalate applied to rat and human abdominal epidermal membranes in vitro. The K_p value obtained using human skin was 2.3 x 10^{-6} cm/hour. The only K_p data available for this compound were obtained with the neat material; no K_p data were available for aqueous solutions, so the K_p data are not included in Table 5-3, and the weight-of-evidence scoring system has not been used to evaluate the K_p value(s).

2,4-Dichlorophenol

Two studies reported values K_p for this compound. The K_p for 2,4-dichlorophenol has been reported by Huq et al. (1986) for hairless mouse skin, and by Roberts et al. (1977) for human skin. The recommended K_p value was reported by Roberts et al. (1977) from in vitro permeability experiments on human abdominal epidermal membranes, yielding a K_p of 10.01 x 10^{-4} cm/minute (= 6.01 x 10^{-2} cm/hour). (See *p*-Bromophenol for details of Roberts et al. [1977].) Epidermal membranes, separated from human abdominal skin, were obtained at autopsy and used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

Di-(2-ethylhexyl) phthalate

Only one study was identified that reported K_p values for this compound (Scott et al., 1987). These investigators obtained K_p values for neat di-(2-ethylhexyl) phthalate applied to rat and human abdominal epidermal membranes in vitro. The value obtained using human skin was 5.7 x 10^{-6} cm/hour. The only K_p data available for this compound were obtained with the neat material; no K_p data were available for aqueous solutions, so the K_p data are not included in Table 5-3 and the weight-of-evidence scoring system has not been used to evaluate the K_p value(s).

Diethyl phthalate

Only one study was identified that reported K_p values for diethyl phthalate (Scott et al., 1987). These investigators obtained K_p values for neat diethyl phthalate applied to rat and human abdominal epidermal membranes in vitro. The K_p value obtained using human skin was 1.14 x 10^{-5} cm/hour. The only K_p data available for this compound were obtained with the neat material; no K_p data were available for aqueous solutions, so the K_p data are not included in Table 5-3 and the weight-of-evidence scoring system has not been used to evaluate the K_p value(s).

2,4-Dimethylphenol

The only K_p for this compound has been reported by Huq et al. (1986) for hairless mouse skin. Experiments were run in vitro using stirred cells maintained at 37°C. The receptor cell contained saline solution (pH = 6.2). The donor cell contained an aqueous solution of 2,4-dimethylphenol (0.5 mg/mL, pH = 6.31), and a K_p of 1.10×10^{-1} cm/hour was reported. Hairless mouse skin was used in this study and the metabolic capacity of the skin had been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 1, continuous flow - 0, infinite dose - 4, and metabolism - 4. Score = $(1 + 0 + 4 + 4) \times 5 = 45$.

Dimethyl phthalate

Two studies reported the dermal permeability of this compound. Both Scott et al. (1987) and Dugard et al. (1984) obtained dermal absorption rate constants for dimethyl phthalate. However, only Scott et al. (1987) reported their results as K_p. The K_p for neat dimethyl phthalate applied to human abdominal epidermal membranes in vitro was 3.32×10^{-5} cm/hour. Scott et al. (1987) also reported a K_p value for this compound applied to rat skin. The only K_p data available for this compound were obtained with the neat material; no K_p data were available for aqueous solutions, so the K_p data are not included in Table 5-3 and the weight-of-evidence scoring system has not been used to evaluate the K_p value(s).

2,4-Dinitrophenol

Two studies reported the dermal permeability of this compound. Jetzer et al. (1986) and Huq et al. (1986) performed a number of in vitro permeability experiments on hairless mouse abdominal skin sections. These two studies originated from the same research team and used the same techniques. The experiments were performed over a range of pH values in both the receptor and donor cells. The receptor contained a saline solution, and the system temperature was maintained at 37°C. A K_p value of 3.15×10^{-3} cm/hour (Huq et al., 1986) was obtained at pH 6.0. However, no absorption of this compound across the skin was observed at experimental conditions (donor and receptor pH values were 7.1 and 7.6, respectively), that more closely matched the exposure scenario

conditions. Therefore, the K_p value, obtained at pH 6.0 (3.15×10^{-3} cm/hour) represents a reporting limit, not an absolute value. Huq et al. (1986) also reported a test conducted with the donor cell pH at 2.0, with an experimental permeability coefficient for whole skin of 1.51×10^{-1} cm/hour and an estimated permeability coefficient of stratum corneum of 2.28×10^{-1} cm/hour. A K_p value of 3×10^{3} cm/hour as an upper limit is recommended. Hairless mouse skin was used in this study and the metabolic capacity of the skin had been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration.
Weight-of-evidence scoring: species - 1, continuous flow - 0, infinite dose - 4, and metabolism - 4.
Score = (1 + 0 + 4 + 4) x 5 = 45.

1,4-Dioxane

Bronaugh (1982) reported a K_p value for 1,4-dioxane of 4.3×10^{-4} (+/- 0.36×10^{-4}) cm/hour. This value was based on in vitro testing using an aqueous vehicle applied to abdominal human epidermal tissue maintained at 32°C. The test area was occluded with parafilm to prevent volatilization of the 1,4-dioxane. Human skin was used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70

Ethanol

The dermal permeability coefficient for ethanol has been determined in four papers (Del Terzo et al., 1986; Behl et al., 1984; Garcia et al., 1980; Scheuplein and Blank, 1973). Scheuplein and Blank (1973) are the only authors that presented their own experimentally derived K_p for ethanol through human epidermis. In vitro experiments conducted at 25°C, using an aqueous solution of ethanol (0.1 M), resulted in a K_p of 0.8×10^{-3} cm/hour. Human abdominal skin obtained at autopsy was used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

2-(2-Ethoxyethoxy) ethanol

The K_p for this compound was reported only by Dugard et al. (1984). The coefficient was determined using whole human abdominal skin, in vitro. The diffusion cell system was maintained at 30°C, and a K_p of 1.32 x 10^{-4} cm/hour was obtained. The only K_p data available for this compound were obtained with the neat material; no K_p data were available for aqueous solutions, so the K_p data are not included in Table 5-3 and the weight-of-evidence scoring system has not been used to evaluate the K_p value(s).

2-Ethoxyethanol

Two studies reported permeability data for this compound. K_p values for 2-ethoxyethanol applied to human skin in vitro have been reported by both Blank et al. (1967) and Dugard et al. (1984). However, only the Blank et al. (1967) study involved application of this compound to the skin in an aqueous vehicle. From the range of K_p values reported by Blank et al. (1967) for 2-ethoxyethanol (2 to 3 x 10^{-4} cm/hour), the upper-bound of this range, 3 x 10^{-4} cm/hour, was selected as the recommended K_p value. Human abdominal skin obtained at autopsy was used, but the metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration.
Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0.
Score = (10 + 0 + 4 + 0) x 5 = 70.

2-Ethoxyethyl acetate

Two studies reported permeability data for this compound. Dugard et al. (1984) obtained a K_p of 8.07 x 10^{-4} cm/hour for 2-ethoxyethyl acetate permeating through human abdominal epidermal membranes in vitro. One other study reporting a dermal absorption rate for this compound was identified in the literature (Guest et al., 1984), but it only reported a flux for the neat compound. The only K_p data available for this compound were obtained with the neat material; no K_p data were available for aqueous solutions, so the K_p data are not included in Table 5-3 and the weight-of-evidence scoring system has not been used to evaluate the K_p value(s).

Ethylbenzene

Four papers reported dermal permeability data for this compound. Dutkiewicz and Tyras (1967) determined the flux of ethylbenzene in an aqueous solution across human skin in vivo. Using a "direct" method, one that involves measuring the disappearance of the compound from the donor solution, these investigators reported average flux data of 118 $\mu g/cm^2/hour$ and 215.7 $\mu g/cm^2/hour$ for ethylbenzene penetrating through the skin from aqueous solutions of average concentrations of 112.0 and 156.2 mg/L, respectively. From these flux rates and aqueous concentrations, it is possible to calculate K_p values under these conditions of 1.05 cm/hour and 1.38 cm/hour, respectively. Although the validity of the direct method developed by these researchers has recently been questioned, the 1.38 cm/hour K_p value is supported by a K_p of 1.33 cm/hour calculated by using an indirect method, yielding a flux value obtained by determining the amount of ethylbenzene absorbed based on the measurement of a urinary metabolite, mandelic acid. Therefore, the 1.38 cm/hour K_p value from this study appears valid, and is selected as the recommended K_p to use in calculating the dermally absorbed dose in water-contact scenarios. The study was conducted on human skin by immersion of the subject's hand into an aqueous solution of ethyl benzene. The amount of chemical absorbed was quantified by measuring its loss from the donor solution, but there is supporting data from body burden measurements. The study does not demonstrate steady-state conditions.

The other dermal absorption rate values are a summary of the Dutkiewicz and Tyras (1967) results reported by Baranowska-Dutkiewicz (1982) and results obtained after applying neat ethylbenzene to rat skin in vitro (Tsuruta, 1982, 1986).

Based on the Dutkiewicz and Tyras (1967) study, the weight-of-evidence scoring is: species - 10, procedure - 4, PBPK model - 0, and steady-state - 0. Score = (10 + 4 + 0 + 0) x 5 = 70.

Ethyl ether

Only one study has been identified that reports a K_p value for ethyl ether (Blank et al., 1967), and the values are especially applicable to water-contact scenarios. Blank et al. (1967) reported a K_p of 1.5 to 1.7 x 10^{-2} cm/hour for ethyl ether applied as an aqueous solution to human abdominal skin in vitro. The upper-bound K_p of 1.7 x 10^{-2} cm/hour is the recommended value for this compound.

Human abdominal skin obtained at autopsy was used, but the metabolic capacity of the skin had not been maintained. The receptor cell did not have the continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

p-Ethylphenol

A single K_p value has been reported for this compound. Roberts et al. (1977) used human abdominal epidermal membranes and a number of aqueous concentrations of *p*-ethylphenol, in vitro, to determine a K_p of 5.81 x 10^{-4} cm/minute (= 3.49 x 10^{-2} cm/hour). (See *p*-Bromophenol for details of Roberts et al. [1977].) Epidermal membranes, separated from human abdominal skin, were obtained at autopsy and used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

Glucose

Only one paper reported a K_p for glucose. This compound is not an environmental pollutant, but is included here as an example of a highly polar organic compound. Ackermann and Flynn (1987) reported a K_p of 9.5 x 10^{-5} cm/hour for glucose in saline solution permeating through the full thickness of hairless mouse abdominal skin in vitro.

Since most compounds enter the circulation via the capillaries present just below the epidermal layer, the use of full thickness skin may result in artificially high estimates of K_p, especially for highly lipophilic compounds whose penetration through the dermis would be impeded by the aqueous nature of this layer. However, since the K_p for glucose permeating only through the dermis (0.29 cm/hour) is about three to four orders of magnitude greater than the value for full thickness skin, it is clear that the epidermis (and probably specifically the stratum corneum) represents the diffusional barrier for this compound, and that the full thickness skin K_p value is valid.

Abdominal skin from the hairless mouse was used, and its metabolic capacity probably had been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 2, continuous flow - 0, infinite dose - 4, and metabolism - 4. Score = (2 + 0 + 4 + 4) x 5 = 50.

Glycerol

Only one paper reported a K_p for glycerol. This compound is not an environmental pollutant, but is included here as an example of a highly polar organic compound. Ackermann and Flynn (1987) reported a K_p of 1.4×10^{-4} cm/hour for glycerol in saline solution permeating through full thickness hairless mouse abdominal skin in vitro.

Since most compounds enter the circulation via the capillaries present just below the epidermal layer, the use of full thickness skin may result in artificially high estimates of K_p, especially for highly lipophilic compounds whose penetration through the dermis would be impeded by the aqueous nature of this layer. However, since the K_p for glycerol permeating only through the dermis (0.41 cm/hour) is about three to four orders of magnitude greater than the value for full thickness skin, it is clear that the epidermis (and probably specifically the stratum corneum) represents the diffusional barrier for this compound, and that the full thickness skin K_p value is valid.

Abdominal skin from the hairless mouse was used, and its metabolic capacity probably had been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 2, continuous flow - 0, infinite dose - 4, and metabolism - 4. Score = (2 + 0 + 4 + 4) x 5 = 50.

Heptanol

Four studies reported a K_p for heptanol, but only two of these presented a value using human epidermal tissue. Scheuplein and Blank (1973) used an aqueous heptanol solution and performed experiments at 25°C. Blank et al. (1967) used similar experimental procedures, but performed the experiments at 30°C. Since the latter temperature is closer to human body temperature and the K_p was produced with in vitro human abdominal epidermal membranes, the K_p of 3.76×10^{-2} cm/hour reported by Blank et al. (1967) is the recommended value. Human abdominal skin obtained at autopsy was used, but the metabolic capacity of the skin was not maintained. The receptor cell did not have the continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

Hexanol

The dermal permeability coefficient for hexanol has been reported in several papers. However, experimentally derived values for human skin were reported only by Bond and Barry (1988) and by Scheuplein and Blank (1973). The Bond and Barry (1988) in vitro abdominal tissue experiments were performed at 31°C, and are therefore more representative of human body temperatures than the 25°C used by Scheuplein and Blank (1973), and the K_p of 2.77×10^{-2} cm/hour is the recommended value. Human abdominal skin obtained at autopsy was used, but the metabolic capacity of the skin had not been maintained. The receptor cell had continuous flow, and the applied dose of hexanol was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 2, infinite dose - 4, and metabolism - 0. Score = (10 + 2 + 4 + 0) x 5 = 80.

Lead Compounds

Lead naphthenate in lubricating oil was tested by Rasetti et al. (1961) using human skin in vivo, yielding a K_p estimate of 2.4×10^{-3} cm/hour. This study cannot be used to support K_p estimates applicable to aqueous vehicles.

Lead acetate was tested by Moore et al. (1980) using a water-alcohol vehicle applied to humans in vivo, yielding a maximum K_p estimate of 4.2×10^{-6} cm/hour. A value of 4×10^{-6} cm/hour is recommended. The quantity of lead absorbed was calculated from blood count, wholebody counts, and urine radioactivity. Steady-state conditions were not verified. Weight-of-evidence scoring: species - 10, procedure - 4, PBPK model - 0, and steady-state - 0. Score = (10 + 4 + 0 + 0) x 5 = 70.

Mercury Compounds

Skog and Wahlberg (1964) investigated the absorption of aqueous solutions of methyl mercurydicyandiamide applied to guinea pig skin in vivo. Flux was reported as μg Hg cm^{-2} hour^{-1}, so the K_p values are calculated on a percentage weight basis for Hg in the methyl mercury dicyandiamide solution. Values of 3.34 x 10^{-3} and 4.39 x 10^{-3} cm/hour are calculated from the flux data provided by Skog and Wahlberg (1964) for mercury in aqueous solutions of 0.04 M and 0.08 M, respectively, of this compound. Skog and Wahlberg (1964) used the disappearance technique to estimate the flux of mercury across guinea pig skin. See Section 3 for a discussion of the limitations of this technique. Methyl mercury dicyandiamide was also tested by Friberg et al. (1961) using an aqueous solution applied in vivo to guinea pigs, yielding a K_p estimate of 1.4 x 10^{-3} cm/hour for the lower concentration tested. A K_p of 1 x 10^{-3} cm/hour is the recommended value for calculating a dermally absorbed dose in water-contact scenarios. The amount of methyl mercury dicyandiamide absorbed was quantified by disappearance measurements. Steady-state conditions were not verified. Weight-of-evidence scoring: species - 4, procedure - 1, PBPK model - 0, and steady-state - 0. Score = (4 + 1 + 0 + 0) x 5 = 25.

Mercuric chloride has been tested by Wahlberg (1965a, 1971) using an aqueous vehicle applied to the guinea pig in vivo, yielding a K_p estimate of 2.5 x 10^{-3} cm/hour. Friberg et al. (1961) also applied an aqueous solution in vivo to guinea pigs, yielding a K_p estimate of approximately 2.1 x 10^{-3} cm/hour for the lower concentration tested. Also, Wahlberg (1965a), using an aqueous solution applied to human skin in vitro, obtained a K_p estimate of 9.3 x 10^{-4} cm/hour. A value of 1 x 10^{-3} cm/hour is recommended. Human mammary skin obtained at surgery was used in this study. The metabolic capacity of the skin had not been maintained, but the applied dose of mercuric chloride had been essentially infinite in concentration. There were continuous flow conditions in the receptor cell. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 2 + 4 + 0) x 5 = 80.

Skog and Wahlberg (1964) investigated the absorption of aqueous solutions of potassium mercuric iodide (K_2HgI_4) applied to guinea pig skin in vivo. Since flux was reported as mμM Hg cm^{-2} hour^{-1}, the K_p was calculated on a percentage weight basis for Hg in the K_2HgI_4 solution. Values ranging from 4.48 x 10^{-3} to 1.05 x 10^{-2} cm/hour were calculated from the flux data provided by Skog and Wahlberg (1964) for Hg in a range of aqueous K_2HgI_4 solutions. K_p values in the middle range of concentrations were all approximately 1 x 10^{-2} cm/hour for the mercuric ion.

Potassium mercuric iodide was also tested by Wahlberg and Skog (1962) using an aqueous solution applied in vivo to guinea pigs, yielding an average K_p estimate of 2.7 x 10^{-3} cm/hour. A value of 3 x 10^{-3} cm/hour is therefore recommended for this compound, potassium mercuric iodide.

In both of these studies (Skog and Wahlberg, 1964; Wahlberg and Skog, 1962) the disappearance technique was used to estimate the flux of mercury across guinea pig skin. See Chapter 3 for a discussion of the limitations of this technique. Steady-state conditions were not verified in either study. Based on the Wahlberg and Skog (1962) study, the weight-of-evidence scoring is: species - 4, procedure - 1, PBPK model - 0, and steady-state - 0. Score = (4 + 1 + 0 + 0) x 5 = 25.

Methanol

Five papers presented K_p values for this compound. The K_p for methanol has been determined for rat skin by Del Terzo et al. (1986) and Behl et al. (1983a), and for mouse skin by Behl et al. (1984). Scheuplein and Blank (1973) presented data for experiments conducted using human abdominal epidermal tissue in an in vitro diffusion apparatus, and loaded the donor compartment with an aqueous methanol solution (0.1 M), yielding a K_p of 0.5 x 10^{-3} cm/hour.

Southwell et al. (1984) used water conditioned stratum corneum of human abdominal skin in vitro and reported a K_p for methanol of 1.6 x 10^{-3} cm/hour. This is the recommended K_p value. The study used human abdominal skin obtained at autopsy. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 +0 + 4 + 0) x 5 = 70.

2-Methoxyethanol

For 2-methoxyethanol, the only K_p reported was from the study by Dugard et al. (1984). A value of 2.89 x 10^{-3} cm/hour was obtained for neat 2-methoxyethanol permeating through human abdominal epidermal membranes tested in vitro at 30°C. The only K_p data available for this compound were obtained with the neat material in vitro; no K_p data were available for aqueous solutions, so the K_p data are not included in Table 5-3 and the weight-of-evidence scoring system has not been used to evaluate the K_p value(s).

2-(2-Methoxyethoxy) ethanol

The only K_p reported for this compound was from the study by Dugard et al. (1984). The coefficient was determined using neat material with whole human abdominal skin, in vitro. The diffusion cell system was maintained at 30°C, and the K_p was determined to be 2.06 x 10^{-4} cm/hour. The only K_p data available for this compound were obtained with the neat material; no K_p data were available for aqueous solutions, so the K_p data are not included in Table 5-3 and the weight-of-evidence scoring system has not been used to evaluate the K_p value(s).

1-Methoxypropan-2-ol

Only one K_p was identified from the literature for this compound. Dugard et al. (1984) obtained a value of 1.25 x 10^{-3} cm/hour for neat 1-methoxypropan-2-ol applied to human skin in vitro tested at 30°C. The only K_p data available for this compound were obtained with the neat material; no K_p data were available for aqueous solutions, so the K_p data are not included in Table 5-3 and the weight-of-evidence scoring system has not been used to evaluate the K_p value(s).

Methyl hydroxybenzoate (unspecified isomer)

A single study was identified that provided a K_p value for this compound. Roberts et al. (1977) obtained a K_p of 1.52 x 10^{-4} cm/minute for methyl hydroxybenzoate permeating the human abdominal epidermal layer in vitro from an aqueous solution. Conversion of this value to a K_p in cm/hour yields 9.12 x 10^{-3} cm/hour. (See *p*-Bromophenol for details of Roberts et al. [1977].)

Epidermal membranes, separated from human abdominal skin, were obtained at autopsy and used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

ß-Naphthol

A single K_p value has been identified for this compound. Roberts et al. (1977) used human epidermal abdominal membranes and a number of aqueous concentrations of ß-naphthol in vitro to determine a K_p of 4.65×10^{-4} cm/minute (= 2.79×10^{-2} cm/hour). (See *p*-Bromophenol for details of Roberts et al. [1977].) Epidermal membranes, separated from human abdominal skin, were obtained at autopsy and used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

Nickel Compounds

Nickel chloride has been tested by Fullerton et al. (1986, 1988) using aqueous solutions applied to human skin in vitro, yielding a K_p estimate of 1×10^{-4} cm/hour. A value of 1×10^{-4} cm/hour is recommended. Human skin was obtained from women undergoing surgery. The metabolic capacity of the skin had not been maintained, as it had been stored at -20°C. The receptor cell did not have continuous flow, but the applied dose of nickel chloride was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

Nickel sulfate has been tested by Fullerton et al. (1986, 1988) and Samitz and Katz (1976) using aqueous solutions applied to human skin in vitro, yielding K_p estimates of $<9 \times 10^{-6}$ cm/hour. A value of 9×10^{-6} cm/hour is recommended. Samitz and Katz used human epidermis obtained at autopsy. The metabolic capacity of the skin had not been maintained, but the applied dose of nickel sulfate had been essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

2-Nitrophenol

Two studies provided K_p values for this compound. The K_p for this compound, 1.01 x 10^{-1} cm/hour, was reported by both Jetzer et al. (1986) and by Huq et al. (1986) for hairless mouse skin. However, the experimental value for the coefficient originated in the Huq et al. (1986) paper. The experiments used whole abdominal mouse skin, in an in vitro stirred cell system maintained at 37°C. The receptor contained saline solution (pH = 6.2). The donor cell was loaded with an aqueous solution of 2-nitrophenol (0.5 mg/mL, pH = 3.46). Huq et al. (1986) used hairless mouse skin, and the metabolic capacity of the skin had been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 1, continuous flow - 0, infinite dose - 4, and metabolism - 4. Score = (1 + 0 + 4 + 4) x 5 = 45.

3-Nitrophenol

A single K_p value has been identified for this compound. Roberts et al. (1977) used human abdominal epidermal membranes and a number of aqueous concentrations of 3-nitrophenol in vitro to determine a K_p of 0.94 x 10^{-4} cm/minute (= 5.64 x 10^{-3} cm/hour). (See *p*-Bromophenol for details of Roberts et al. [1977].) Epidermal membranes, separated from human abdominal skin, were obtained at autopsy and used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

4-Nitrophenol

Four papers provided K_p data for this compound. Jetzer et al. (1986), Jetzer et al. (1988), and Huq et al. (1986) performed a number of in vitro experiments using hairless mouse abdominal skin. The recommended K_p, 5.58 x 10^{-3} cm/hour, based on a value of 0.93 x 10^{-4} cm/minute, comes from work by Roberts et al. (1977) who used human epidermal tissues. (See *p*-Bromophenol for details of Roberts et al. [1977].) Epidermal membranes, separated from human abdominal skin, were obtained at autopsy and used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

n-Nitrosodiethanolamine

Bronaugh et al. (1981) reported a K_p value for n-nitrosodiethanolamine of 5.5×10^{-6} (+/- 0.9×10^{-6}) cm/hour. This value was based on in vitro testing using an aqueous vehicle applied to abdominal human epidermal tissue maintained at 32°C. The test area was occluded with parafilm to prevent volatilization of the n-nitrosodiethanolamine. Human abdominal skin obtained at autopsy was used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

Nonanol

The only K_p value identified for nonanol was reported by Scheuplein and Blank (1973). The in vitro experiments used human abdominal epidermal tissues and an aqueous solution of nonanol (1.4×10^{-3} m/L), yielding a K_p value of 6.0×10^{-2} cm/hour. Human abdominal skin obtained at autopsy was used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

Octanol

Five papers presented permeability data for this compound. The K_p for octanol has been determined by three researchers (DelTerzo et al., 1986; Behl et al., 1984; Garcia et al., 1980) using rat or mouse skin. Southwell et al. (1984) and Scheuplein and Blank (1973) reported the only experimentally derived octanol K_p values using human skin, and both studies performed in vitro testing. Similar equipment and experimental conditions were used by both groups, however, Southwell et al. (1984) used well-hydrated skin. The K_p values reported in both papers are similar, 6.1×10^{-2} cm/hour in Southwell et al. (1984) versus 5.2×10^{-2} cm/hour in Scheuplein and Blank (1973), but the value presented by Southwell et al. (1984) is recommended for use because of the skin hydration conditions and because the value represents a newer data set. The study used human abdominal skin obtained at autopsy. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 +0 + 4 + 0) x 5 = 70.

Parathion

Three studies reported permeability data for this compound. Although parathion is one of the most widely studied dermal penetrants, only Knaak et al. (1984b) reported K_p values for this compound, and no studies involved the application of aqueous solutions of parathion. Knaak et al. (1984b) calculated K_p values for parathion applied to rat skin in vivo for adult male and female animals, based either on the $t_{1/2}$ for plasma elimination of the compound or the $t_{1/2}$ for loss of parathion from the skin (see Chapter 3 for a description of this technique). Since water tends to accelerate the uptake of compounds across the skin (see Chapter 2), K_p values for neat parathion probably underestimate the K_p that would be expected for an aqueous solution of parathion.

Flux values are also available from the studies by Frederickson (1961a, b). However, since the absorption rates were determined indirectly as a function of the rate of acetylcholinesterase inhibition, it is unclear whether these values represent the rate of parathion absorption, or the absorption of parathion and its subsequent conversion to its active metabolite, paraoxon.

At least 12 other studies have been conducted which reported percent absorbed values for parathion. Although flux values can theoretically be derived from these data, none of the studies used aqueous solutions of parathion, and therefore, they each have limited use for water-contact scenarios. The only K_p data available for this compound were obtained with the neat material; no K_p data were available for aqueous solutions, so the K_p data are not included in Table 5-3 and the weight-of-evidence scoring system has not been used to evaluate the K_p value(s).

Pentanol

Scheuplein and Blank (1973) reported the only experimentally derived data for the K_p value of pentanol. The in vitro experiments used human abdominal epidermal tissue and were performed at 25°C using an aqueous solution of pentanol (0.1 M). The K_p was determined to be 6.0 x 10^{-3} cm/hour. Human abdominal skin obtained at autopsy was used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

Phenol

Six papers presented permeability data for this compound. Experimentally derived K_p values for phenol were presented by a number of researchers using mouse skin (Huq et al., 1986; Jetzer et al., 1986, 1988; Behl et al., 1983b). Experiments using human skin were performed by Southwell et al. (1984) and Roberts et al. (1977). Southwell et al. (1984) used a 1% (w/v) aqueous phenol solution penetrating in vitro through human abdominal stratum corneum at 22°C, and calculated a mean steady-state flux = 1.49 $\mu g/cm^2/hour$ (K_p calculated as 1.49 x 10^{-4} cm/hour). Roberts et al. (1977) used a number of aqueous phenol concentrations in vitro for human abdominal epidermal membranes, yielding a K_p of 1.37 x 10^{-4} cm/minute (= 8.22 x 10^{-3} cm/hour). (See *p*-Bromophenol for details of Roberts et al. [1977].) Because it is a higher value than the K_p obtained in the Southwell et al. (1984) study, and was obtained with more dilute solutions and higher temperatures (more closely approximating human body temperatures), the K_p obtained in the Roberts et al. (1977) study is recommended when calculating the dermally absorbed dose of phenol. Epidermal membranes, separated from human abdominal skin, were obtained at autopsy and used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration.

Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

Propanol

K_p values for aqueous solutions of propanol penetrating human abdominal epidermal membranes in vitro have been reported in two papers (Blank et al., 1967; Scheuplein and Blank, 1973). Experiments were performed at 30°C by Blank et al. (1967) and are, therefore, more representative of water-contact scenarios than the 25°C tests used by Scheuplein and Blank (1973). The K_p reported by Blank et al. (1967) was 1.7×10^{-3} cm/hour. Human abdominal skin obtained at autopsy was used, but the metabolic capacity of the skin was not maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration . Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

Resorcinol

A single K_p value has been identified for this compound. Roberts et al. (1977) used human abdominal epidermal membranes and a number of aqueous concentrations of resorcinol in vitro, yielding a K_p of 0.04×10^{-4} cm/minute (= 2.4×10^{-4} cm/hour). (See *p*-Bromophenol for details of Roberts et al. [1977].) Epidermal membranes, separated from human abdominal skin, were obtained at autopsy and used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

Silver Compounds

Silver nitrate was tested by Skog and Wahlberg (1964) using an aqueous solution applied to guinea pig skin in vivo, yielding a K_p estimate of $<6.5 \times 10^{-4}$ cm/hour. Similar results were obtained applying an aqueous solution to human skin in vivo, $K_p = <3.5 \times 10^{-4}$ cm/hour (Norgaard, 1954). A K_p value of 6×10^{-4} cm/hour is recommended. The recommended K_p was from a study conducted on human skin in vivo. The amount of silver nitrate absorbed was quantified by disappearance measurements. Steady-state conditions were not verified. Weight-of-evidence scoring: species - 10, procedure - 1, PBPK model - 0, and steady-state - 0. Score = (10 + 1 + 0 + 0) x 5 = 55.

Styrene

Eight papers presented permeability data for this compound. Several of the studies provided flux values for neat styrene permeating as a liquid (Tsuruta, 1982, 1986) or as a vapor (Riihimaki and Pfaffli, 1978; McDougal et al., 1987, 1990) across the skin; however, only the study by Dutkiewicz and Tyras (1968) reported values for the absorption of styrene from an aqueous vehicle. The researchers conducted in vivo tests with humans and reported flux values of 40 to 180 $\mu g/cm^2$/hour for mean aqueous concentrations for 66.5 to 269 mg/L of styrene. This information allows calculation of a K_p of 0.60 (lower-bound) to 0.67 (upper-bound) cm/hour for styrene. Although the lower value may be more appropriate for these water-contact scenarios because the concentration used in the study more closely approximates the concentration of styrene found in drinking- or surface-water supplies, the higher value was selected to give a slightly more conservative estimate of the absorbed dose.

Little information was reported by Dutkiewicz and Tyras (1968) in this brief communication regarding the conditions under which the study was conducted, other than to state the method was developed previously by these researchers (Dutkiewicz and Tyras, 1967). The amount of styrene absorbed was apparently quantified by monitoring the amount of mandelic acid excreted in the urine, and not solely by measuring the loss of the compound from the donor solution; thus, more confidence can be placed in the validity of the flux values as having been calculated from the actual absorbed dose. The study was conducted using human skin of the hand and forearm, and the amount of styrene absorbed apparently was quantified by measuring the amount of the metabolite in the urine. Steady-state conditions were not verified. Weight-of-evidence scoring: species - 10, procedure - 4, PBPK model - 0 and steady-state - 0. Score = (10 + 4 + 0 + 0) x 5 = 70.

Tetrachloroethylene

Bogen et al. (1992) measured percutaneous absorption in hairless guinea pigs exposed for 70 minutes to a dilute aqueous solution of tetrachloroethylene. An airtight glass chamber was used with no head space. Dermal uptake was estimated using a disappearance procedure consisting of comparing the rate of radiolabel loss from chamber water in systems with and without experimental animals. Radiolabel in urine and feces excreted after the experiment was completed was measured and expressed as a fraction of the radiolabel lost from the chamber. The mean value of this fraction did not differ significantly from that obtained using animals injected with a known dose of the compound. Thus, body burden measurements were used to confirm the accuracy of the disappearance procedure. On this basis, a weight-of-evidence score of 4 was deemed appropriate for the procedure. A K_p estimate of 0.37 cm/hour was estimated under steady-state conditions. Weight-of-evidence scoring: species - 4, procedure - 4, PBPK model - 0, and steady-state - 3. Score = $(4 + 4 + 0 + 3) \times 5 = 55$.

Thiourea

Only one study reported a K_p for this compound. This compound is not an environmental pollutant, but is included here as an example of a highly polar compound. Ackermann and Flynn (1987) reported a K_p of 9.6×10^{-5} cm/hour for thiourea in saline solution permeating through full thickness of hairless mouse abdominal skin in vitro.

Since most compounds enter the circulation via the capillaries present just below the epidermal layer, the use of full thickness skin may result in artificially high estimates of K_p, especially for highly lipophilic compounds whose penetration through the dermis would be impeded by the aqueous nature of this layer. However, since the K_p for thiourea permeating only through the dermis (0.62 cm/hour) is about three to four orders of magnitude higher than the value for full thickness skin, it is clear that the epidermis (and probably especially the stratum corneum) represents the diffusional barrier for this compound, and that the full thickness skin K_p value is valid.

Abdominal skin from the hairless mouse was used, and its metabolic capacity probably had been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 2, continuous flow - 0, infinite dose - 4, and metabolism - 4. Score = (2 + 0 + 4 + 4) x 5 = 50.

Thymol

Only a single K_p value has been identified for this compound. Roberts et al. (1977) used human abdominal epidermal membranes and a number of aqueous concentrations of thymol in vitro, yielding a K_p of 8.8×10^{-4} cm/minute (= 5.28×10^{-2} cm/hour). (See *p*-Bromophenol for details of Roberts et al. [1977].) Epidermal membranes, separated from human abdominal skin, were obtained at autopsy and used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

Toluene

K_p data for toluene were presented in seven papers. However, only Dutkiewicz and Tyras (1968) and Baranowska-Dutkiewicz (1982) used aqueous solutions. In vivo tests with human skin yielded a K_p value of 1.01 cm/hour, which can be both read from the graph plotting the rate of absorption against concentration (Dutkiewiez and Tyras, 1968) and calculated from the flux data of Baranowska-Dutkiewicz (1982). The studies were conducted on the skin of the hand and forearm in man and the amounts of styrene absorbed were quantified by measuring the loss of the compound from the donor solution. Steady-state conditions were not verified. Weight-of-evidence scoring: species - 10, procedure -1, PBPK model - 0 and steady-state - 0. Score = (10 + 1 + 0 + 0) x 5 = 55.

Trichloroethylene

Bogen et al. (1992) measured percutaneous absorption in hairless guinea pigs exposed for 70 minutes to a dilute aqueous solution of trichloroethylene. An airtight glass chamber was used with no head space. Dermal uptake was estimated using a disappearance procedure consisting of comparing the rate of radiolabel loss from chamber water in systems with and without experimental animals.

Radiolabel in urine and feces excreted after the experiment was measured and expressed as a fraction of the radiolabel lost from the chamber. The mean value of this fraction did not differ significantly from that obtained using animals injected with a known dose of the compound. Thus, body burden measurements were used to confirm the accuracy of the disappearance procedure. On this basis, a weight-of-evidence score of 4 was deemed appropriate for the procedure. A K_p estimate of 0.23 cm/hour was estimated under steady-state conditions. Weight-of-evidence scoring: species - 4, procedure - 4, PBPK model - 0, and steady-state - 3. Score = (4 + 4 + 0 + 3) x 5 = 55.

2,4,6-Trichlorophenol

Two studies presented K_p values for this compound. The permeability of aqueous 2,4,6-trichlorophenol was reported for in vitro tests with mouse skin by Huq et al. (1986) and human skin by Roberts et al. (1977). The recommended K_p value is therefore based on the human permeability test data. Experiments by Roberts et al. (1977) were performed in vitro, at 25°C, using abdominal epidermal tissue and a stirred distilled water receptor. The donor compartments were loaded with a number of different concentrations of aqueous solutions of 2,4,6-trichlorophenol, yielding a K_p value of 9.9×10^{-4} cm/minute (= 5.9×10^{-2} cm/hour). Epidermal membranes, separated from human abdominal skin, were obtained at autopsy and used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

Urea

Only one study presented K_p values for urea. This compound is not an environmental pollutant, but is included here as an example of a highly polar compound. Ackermann and Flynn (1987) reported a K_p of 1.2×10^{-4} cm/hour for urea in saline solution permeating through full thickness of hairless mouse abdominal skin in vitro.

Since most compounds enter the circulation via the capillaries present just below the epidermal layer, the use of full thickness skin may result in artificially high estimates of K_p, especially for highly lipophilic compounds whose penetration through the dermis would be impeded by the aqueous nature of this layer. However, since the K_p for urea permeating only through the dermis (0.68 cm/hour) is about three to four orders of magnitude higher than the value for full thickness skin, it is clear that the epidermis (and probably specifically the stratum corneum) represents the diffusional barrier for this compound, and that the full thickness skin K_p value is valid.

Abdominal skin from the hairless mouse was used, and its metabolic capacity probably had been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration. Weight-of-evidence scoring: species - 2, continuous flow - 0, infinite dose - 4, and metabolism - 4. Score = (2 + 0 + 4 + 4) x 5 = 50.

Water

Seven studies presented K_p values for this compound. Permeability coefficients for water have been obtained for several species including humans. In fact, the range of "normal" values for the K_p of water through human skin has been so well characterized that K_p values $>2.5 \times 10^{-3}$ cm/hour are suggestive of skin damage. Bronaugh et al. (1986b) pointed out that most K_p values for human skin in vitro have ranged historically from 0.5×10^{-3} to 2.5×10^{-3} cm/hour. From their extensive study, using skin from individuals of both sexes that span a broad range of ages, Bronaugh et al. (1986b) reported an average K_p value of 1.55×10^{-3} cm/hour. This value is recommended as the K_p for water.

Human K_p values for water reported by Bond and Barry (1988) and Bronaugh and Stewart (1986) are essentially identical to this average value. Values for the K_p of water across animal skin from in vitro tests range from being very similar to human skin to being about 3 to 8 times greater (e.g., 0.6 to 3.2×10^{-3} cm/hour for hairless mouse skin as reported by Behl et al. (1984) to 11.7×10^{-3} for the Swiss mouse as reported by DelTerzo et al. (1986).

Bronaugh et al. (1986b) tested human epidermis prepared from full thickness abdominal skin, obtained at autopsy. The metabolic capacity of the skin had not been maintained in this study, but the receptor cell had continuous flow and the applied dose was essentially infinite in concentration. Weight-of-evidence scoring: species - 10, continuous flow - 2, infinite dose - 4, and metabolism - 0. Score = (10 + 2 + 4 + 0) x 5 = 80.

3,4-Xylenol

Only one identified paper has reported a K_p value for 3,4-xylenol. Roberts et al. (1977) performed a series of experiments using a number of concentrations of aqueous solutions of 3,4-xylenol, and human abdominal epidermal tissue in an in vitro system consisting of a stirred distilled water receptor at 25°C. The K_p value was reported to be 6.0 x 10^{-4} cm/minute (= 3.6 x 10^{-2} cm/hour). (See *p*-Bromophenol for details of Roberts et al. [1977].) Epidermal membranes, separated from human abdominal skin, were obtained at autopsy and used in this study. The metabolic capacity of the skin had not been maintained. The receptor cell did not have continuous flow, but the applied dose of the chemical was essentially infinite in concentration.
Weight-of-evidence scoring: species - 10, continuous flow - 0, infinite dose - 4, and metabolism - 0. Score = (10 + 0 + 4 + 0) x 5 = 70.

Zinc Compounds

Zinc chloride was tested by Skog and Wahlberg (1964) using an aqueous solution applied to guinea pig skin in vivo yielding a K_p estimate of 6.5 x 10^{-4} cm/hour. Thus, a K_p value of 6 x 10^{-4} cm/hour is recommended. Skog and Wahlberg (1964) tested guinea pig skin in vivo and quantified the amount of zinc chloride absorbed by disappearance measurements. Steady-state conditions were not verified. Weight-of-evidence scoring: species - 4, procedure - 1, PBPK model - 0, and steady-state - 0. Score = (4 + 1+ 0 + 0) x 5 = 25.

Zinc oxide was tested by Agren (1990) using an ointment dressing (assumed to be an oil based substance) applied to human skin in vivo, yielding a K_p estimate of 8 x 10^{-3} cm/hour. This study cannot be used to support a K_p estimate applicable to aqueous vehicles for water-contact scenarios.

6. DERMAL ABSORPTION OF COMPOUNDS FROM SOIL

Dermal contact with contaminated soil represents a potentially significant route of exposure to toxic compounds. For example, workers at industrial facilities or hazardous waste sites can be exposed to soil contaminated directly during the manufacture, transport, storage, or disposal of such compounds. The general population can be exposed to compounds applied directly to soil, as in the case of pesticides applied to lawns and gardens. The general population may also be exposed to soil that is contaminated indirectly as a result of wind erosion, surface water runoff, or fallout from municipal incinerators, smelters, and other such sources. Therefore, soil can become contaminated from various sources, and activities such as playing in the dirt or gardening can result in exposure of different segments of the general population to contaminated soil.

A number of methodologies have been developed to estimate the exposure of an individual to toxic compounds in a soil matrix. While some approaches are designed to estimate dermal exposure (e.g., EPA, 1986), others include an absorption factor to permit the calculation of absorbed dose (e.g., EPA, 1984b; Kimbrough et al., 1984; Paustenbach et al., 1986; Eschenroeder et al., 1986; EPA, 1989b). For most chemicals, the parameters in these approaches have not been well characterized. Estimates of the amount of soil adhering to human skin are reported in Chapter 8. However, major uncertainties exist in the extent to which a chemical is percutaneously absorbed and in the extent to which a chemical will partition from soil to skin. In addition to being chemical-dependent, percutaneous absorption of a chemical in a soil matrix may depend on characteristics of the soil, such as particle size and organic carbon content, which affect partitioning of the chemical between soil and skin. If percutaneous absorption is reported as the fraction of applied dose that is absorbed, the amount of soil adhering to the skin determines the size of the applied dose and hence affects the fraction absorbed.

The available experimental data and the factors that affect percutaneous absorption of compounds from soil are examined in this chapter. Data which may be used to estimate absorption are considered, and theoretical models for estimating absorption from soil are discussed.

6.1. FACTORS AFFECTING THE DERMAL (PERCUTANEOUS) ABSORPTION OF COMPOUNDS FROM SOIL

For purposes of developing criteria for reviewing experimental data on soil absorption, it is instructive to review some principles of dermal absorption. Absorption of chemicals through the skin is thought to occur primarily via diffusion. Under ideal conditions (i.e., steady-state, homogenous media, etc) diffusion can be modeled with Fick's first law. In spite of the lack of such ideal conditions, Fick's first law is generally accepted as a useful way to understand the dynamics of dermal absorption of compounds in neat form and in aqueous media. Dermal absorption of compounds from soil is complicated by processes occurring in the soil such as desorption from and diffusion through the soil. Thus, more complex models are desirable to model dermal absorption from soil. As discussed later in this chapter, some investigators have begun development of such models, and these may ultimately be the best guides to reviewing experimental data. Meanwhile, however, Fick's first law can be used to address this issue. In situations where diffusion through the skin is the rate limiting step in the process, it should provide valid insight. By keeping in mind its limitations in other situations, such as those where volatilization is believed to compete strongly with the dermal absorption process, the error in its use can be minimized.

Fick's first law states that flux is equal to the concentration gradient times a constant termed diffusivity. Assuming that the contaminant concentration under the skin is negligible due to removal by the blood circulation, the concentration gradient can be approximated as the contaminant concentration on the outer skin surface divided by the skin thickness, yielding the following relationship:

$$J_{ss} = C_{soil}\, \rho_{soil} \frac{D_s\, K_{s/soil}}{l_s} \tag{6.1}$$

where:

J_{ss} = Flux (mg/cm^2-hour)
C_{soil} = Concentration of contaminant in soil (mg/kg) x (10^{-6} kg/mg)

ρ_{soil} = Density of soil (mg/cm^3)

D_s = Diffusivity of the chemical in skin (cm^2/hr)

$K_{s/soil}$ = Skin/soil partition coefficient (unitless)

l_s = Skin thickness (μm) x (10^{-4} cm/μm)

Since the fraction of the applied dose absorbed is the absorbed dose divided by the applied dose, the absorption fraction can be expressed as follows:

$$ABS = \frac{J_{ss}\, t_{event}\, A}{C_{soil}\, AF\, A} = \frac{C_{soil}\, \rho_{soil}\, t_{event}\, \frac{D_s}{l_s}}{C_{soil}\, AF} K_{s/soil} = \frac{\rho_{soil}\, t_{event}\, \frac{D_s}{l_s}}{AF} K_{s/soil} \tag{6.2}$$

where:

ABS = Absorption fraction (unitless)

t_{event} = Exposure time per event (hour/event)

A = Skin surface area available for contact (cm^2)

AF = Soil to skin adherence factor (mg/cm^2-event)

Equation (6.2) suggests that the absorption fraction is directly proportional to diffusivity and time, inversely proportional to skin thickness and soil loading, and independent of concentration and area. In order to design experiments that provide estimates transferable to human exposure conditions, the experimental conditions should match the expected human exposure conditions in terms of these properties. The implications of this are discussed below for each of these four properties.

Diffusivity is recognized to be a function of both the contaminant and the diffusion medium, in this case, human skin. The skin thickness used in the experiment should match that of human skin. The importance of these skin dependent factors underscores the desirability of using human skin in experiments. Since the skin of many animal species is thinner than human skin, use of animal skin may lead to overestimates of dermal absorption.

The experiment should provide absorption estimates over a time corresponding to the time that soil is likely to remain on skin during actual human exposures. Experiments longer than 24 hours are likely to overestimate absorption. Many investigators use an exposure period of 24 hours. Although Fick's first law suggests that absorption is directly proportional to exposure time, linear adjustments may not be accurate, since it is unknown how soon steady-state is established and since steady-state conditions may not be maintained throughout the experiment due to mass balance constraints.

The amount of soil applied to the skin is critical to consider when interpreting experimental data to derive absorption fractions. Holding all exposure conditions constant except soil application (AF), Equation (6.2) suggests that as AF decreases, flux should remain constant and the absorption fraction (ABS) therefore should increase. Investigators developing models of percutaneous absorption of chemicals from soil have also observed that the fraction of the dose absorbed should decrease as the thickness of the soil layer increases (Kissel and McAvoy, 1989; McKone, 1990).

Experimentalists in the field speculate that below some soil loading the flux will begin to decline (EPA Workshop on Dermal Exposure. April 2 and 3, 1991. Herndon, VA. Sponsored by Office of Health and Environmental Assessment, Washington, DC, hereafter referred to as EPA Workshop on Dermal Exposure). An explanation for this decline is that at low soil loadings the skin may not be completely covered with soil particles, making less contaminant available for absorption. This concept is sometimes referred to as the "monolayer theory", where the monolayer is defined as a single layer of tightly packed particles. At soil applications less than a monolayer, space between the particles increases resulting in incomplete coverage of the skin and lower flux rates. Assuming that the reductions in flux (at loadings less than the monolayer) occur in proportion to the reductions in loading (as is suggested by the coverage explanation) then the absorption fraction observed for the monolayer loading should be similar to that at lower loadings. The soil loading that corresponds to a monolayer has not been well established and is likely to vary according to the soil density and the distribution of particles by size. Assuming soil particles have an average diameter of 100 μm and density of 1500 mg/cm^3, a monolayer of about 8 mg/cm^2 is predicted.

Based on judgement and unpublished experimental observations, the experts at the EPA Workshop on Dermal Exposure identified 5 mg/cm^2 as their best estimate of the loading that corresponds to a monolayer and below which the flux begins to decline. They further agreed that the ABS observed at this loading would probably be similar to that observed at soil loadings expected under actual human exposure conditions (i.e., 0.2 to 1 mg/cm^2). One approach to dealing with the variability in soil application would be to adjust the measured ABS to the ABS which would have been observed for an application of 5 mg soil/cm^2 as indicated below:

$$\text{Scaled ABS} = (\text{ABS at loading AF})(\text{AF}/5) \tag{6.3}$$

The literature on experimental data is inconclusive as to the appropriateness of Equation (6.3). The results of Yang et al. (1989) appear to support the need for adjustment according to soil application. Yang et al. (1989) measured absorption of BaP applied to rat skin in vitro in either 9 mg soil/cm^2 or 56 mg soil/cm^2. The concentration of BaP was 1 ppm in both experiments. Only the amount of soil, and consequently the dose of BaP, was varied. The amount of BaP absorbed after 96 hours was 1.3 ng in both experiments. The percentages absorbed were 8.4% of the BaP applied in 9 mg soil/cm^2 and 1.3% of the BaP applied in 56 mg soil/cm^2.

The work of Wester and colleagues, however, raises questions about whether using Equation (6.3) is appropriate. Wester et al. (1991) measured similar percentages of cadmium chloride absorbed from applications in 20 mg soil/cm^2 and 40 mg soil/cm^2. In a study of BaP, moreover, Wester et al. (1990a) reported an average absorption of 13.2% of 10 ppm BaP applied in 40 mg/cm^2 in 4 rhesus monkeys over 24 hours. Adjustment of the soil application rate in Wester et al. (1990a) using Equation (6.3) to reflect a soil loading of 5 mg/cm^2 indicates 24 hour absorption in the monkey of 100% of the applied dose, which is higher than absorption of neat BaP observed in any species (Yang et al., 1986a, 1989; Kao et al., 1984, 1985, 1988; Bronaugh and Stewart, 1986), although absorption of 82% to 93% of applied dose was observed in the mouse for a high dose over a 7 day exposure period and for lower doses over 24-hour periods (Sanders et al., 1984). Comparison of the absorption of BaP in mouse, human, rat, rabbit, guinea pig, and marmoset skin showed the mouse skin to be about 3 times more permeable than human skin and 2.5 to 5 times more permeable than that of the other species (Kao et al., 1985).

There are few studies on the absorption of chemicals from a soil matrix, and insufficient evidence to support the application of Equation (6.3) to the existing experimental data at this time. Obviously, much uncertainty surrounds these recommendations, and further research on the influence of soil loadings on flux is strongly recommended.

As noted above, volatilization can compete with the dermal absorption process. Thus, experimental results for volatile compounds should not be used in exposure assessments when the experimental conditions restrict volatilization. This means that experiments should be conducted at ambient temperatures and that the soil should not be covered in a manner that limits volatilization.

Chapters 2 and 3 recommend studying aqueous permeability coefficients using both in vivo and in vitro techniques. As discussed in Chapter 5, human in vitro experiments should ideally be confirmed by animal in vivo experiments. The rationale for this approach is that the in vitro experiments allow the use of human skin and are more easily controlled and reproduced. However, they may not accurately mimic blood flow, metabolism, and other pharmacokinetic processes in living systems. Thus ideally, the in vitro experiments should be used as the primary means of studying dermal absorption, but validated with in vivo experiments. These same principles should apply to dermal absorption from soil. Where in vitro and in vivo experiments on the same contaminant suggest significantly different results, judgement should be used to decide which is more reliable, and the selected value must be characterized as much more uncertain than values supported by both approaches. An alternative approach for resolving differences in the results of in vitro and in vivo experiments, where sufficient data are available for a particular compound, is to adjust the absorption fraction (ABS) as follows:

$$\text{Human in vivo ABS} = \frac{(\text{Human in vitro ABS})(\text{Species A in vivo ABS})}{(\text{Species A in vitro ABS})} \tag{6.4}$$

This approach assumes that the ratio of in vivo to in vitro measured absorption fractions for a particular contaminant will be the same in humans as in animal species. The validity of this approach depends on similarities in skin structure and pharmacokinetic processes between animals and humans.

The factors outlined in Chapters 2 and 3 are known to affect the absorption of neat compounds and compounds in aqueous or organic solvents. Presumably, these factors have the potential to influence the absorption of soil-bound compounds as well. For example, Skowronski et al. (1989) proposed skin temperature and exposed surface area, soil pH, and soil moisture content as factors that can affect the desorption of organic compounds from soil and subsequent uptake across the skin. Factors unique to the soil matrix, such as the physical and chemical characteristics of the soil, and the chemical's propensity for binding to soil particles, have been shown to affect the dermal bioavailability of a soil-bound compound.

Roy and colleagues reported an eightfold reduction in the percent of TCDD absorbed through rat skin in vitro when the compound was applied in soil with high organic carbon content (11.22%) as compared to application in soil of low organic carbon content (0.45%) (EPA, 1991; Roy et al., 1990). The properties of the soils used in this study are summarized in Table 6-1. By contrast, Poiger and Schlatter (1980) reported that 0.05% or less of a dose of TCDD applied to the skin of rats in an activated carbon/water paste was found in the liver after 24 hours of exposure compared to about 2% of TCDD applied in a soil/water paste. These results suggest that the TCDD is even more strongly adsorbed to activated carbon than to soil. Although TCDD in the soil was bioavailable, essentially none of the TCDD was bioavailable when applied in activated carbon.

Poiger and Schlatter (1980) have shown that aging of TCDD in soil before oral administration of a TCDD/soil paste to rats affected the percentage of the applied dose that appeared in the liver. Ingestion of soil aged with TCDD for 10 to 15 hours before oral administration resulted in 24.1% of the dose appearing in the liver; only 16% of the dose appeared in the liver after ingestion of soil aged with TCDD for 10 days before oral administration. The authors postulate that the decreased oral bioavailability that occurs as a function of soil contact time with TCDD is probably the result of a "strengthening" of the binding of TCDD to soil particles. From these two time points, it is not possible to extrapolate the uptake of TCDD that would occur after longer contact times with soil, nor is it possible to determine how these results might be applicable to dermal uptake of TCDD. However, it is significant to note that Shu et al. (1988) reported little difference in the percent of dose appearing in the liver of rats dermally exposed to soil contaminated with TCDD in the laboratory (contact time unreported, but presumably on the order of hours to days) and soil from Times Beach, Missouri, that contained an equivalent amount of TCDD and was presumably contaminated many years before the study was conducted.

Table 6-1. Properties of Soil Used in the Studies of Dermal Absorption of TCDD from Two Types of Soil

	Hyde Soil	Chapanoke Soil
Sand (%)	19.5	15.1
Silt (%)	70.1	68.2
Clay (%)	10.4	16.7
Organic carbon content (%)	11.2	0.4
Particle Size (mm)		
0.05 - 0.1 (%)	59.5	67.5
0.1 - 0.25 (%)	19.5	18.5
0.25 - 0.5 (%)	15.9	11.3
0.5 - 1.0 (%)	4.1	2.0
1.0 - 2.0 (%)	1.0	0.1

Source: EPA (1991)

Poiger and Schlatter (1980) and Shu et al. (1988) showed that the concentration of TCDD in the soil matrix, within the range of concentrations studied, had little effect on the percentage of the applied dose that was subsequently absorbed and appeared in the liver, provided the amount of soil applied to the skin was constant. The amount of TCDD in the liver increased, however, in direct proportion to the concentration.

The capacity of one component of a mixture of soil-adsorbed compounds to impede or accelerate the absorption of another component has been studied to a limited degree. Shu et al. (1988) demonstrated that co-contamination of soil with TCDD and various concentrations of waste crankcase oil had little effect on the dermal bioavailability of soil-adhered TCDD. Given the potential for numerous contaminants to co-exist in soil, this factor requires further study to understand its impact on percutaneous absorption.

The above discussion presents conditions that may affect the rate of percutaneous absorption and the strategy used to review and interpret the experimental data on dermal absorption from soil. Considering the limited number of compounds that have been studied, it was deemed premature to develop a formal weight-of-evidence scheme analogous to that for aqueous compounds. However, it is important to convey the uncertainty in the estimated absorption fractions. Accordingly, the above strategy was used to develop a best estimate of the absorption fraction, and an indication of the possible range of uncertainty surrounding this estimate was derived from alternative interpretations of the data.

6.2. USING EXPERIMENTALLY DERIVED VALUES

Experimentally derived values of percutaneous absorption from soil, expressed as the percentage of the applied dose absorbed, have been found for nine chemicals -- 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (EPA, 1991), 3,3′,4,4′-tetrachlorobiphenyl (TCB) (EPA, 1991), benzo[a]pyrene (BaP) (Wester et al., 1990a; Yang et al., 1989), DDT (Wester et al., 1990a), cadmium (Wester et al., 1991), benzene (Skowronski et al., 1988), toluene (Skowronski et al., 1989), xylene (Skowronski et al., 1990), and hexadecane (Kissel, J.C. and Duff, R. [Mass transfer of soil on skin. Poster Presentation. Measuring, Understanding, and Predicting Exposure in the 21st Century. Atlanta, GA. November 18-21, 1991]). These experimental values can seldom be used directly in exposure assessments because the experimental conditions are usually not completely consistent with exposure conditions in the environment. Consequently, the results of each study must be scrutinized in light of the assumptions of the exposure assessment, and the experimental results must be adjusted to reflect likely percutaneous absorption under the conditions of the exposure assessment. Issues which must be considered when using experimental data in exposure assessments include the following:

- Using in vitro experimental results to predict in vivo percutaneous absorption.
- Using animal data to predict percutaneous absorption in humans.
- Differences in quantity of soil applied in the experiment and the amount of soil contact assumed in the exposure assessment.
- Differences in the exposure duration used in the experiment and the amount of time an individual is likely to be exposed to soil.

These issues were addressed as follows:

- Roy and colleagues studied percutaneous absorption of TCDD and TCB in rat and human skin in vitro and in rats in vivo (EPA, 1991). Human in vivo percutaneous absorption can be estimated from these data using Equation (6.4).
- Where data were not available to allow correction for uncertainties introduced by using animal models and in vitro test systems, the fractions absorbed in the experiments are reported without such corrections.
- Soil applications expected in actual exposures are on the order of 0.2 mg/cm^2 to 1 mg/cm^2 rather than the 6 mg/cm^2 to 40 mg/cm^2 used in the studies. However, the extent to which these loadings affected the bioavailability and hence the percent absorbed is unclear. Therefore, the experimental data were reported without correction.
- Recommended values are presented based on 24-hour or 16-hour experimental results. Exposure durations in the studies of TCDD and TCB conducted by Roy and colleagues were 96 hours. However, sufficient information was available on 24-hour absorption to allow an estimate of fractions absorbed at 24 hours (EPA, 1991).
- Where a range of results is available because of use of different animal models, test systems, or soil types and no value in the range is clearly preferable, the results are reported as a range.

Table 6-2 is a summary of the experimental conditions and results obtained from studies of TCDD, TCB, BaP, DDT, and cadmium. Table 6-3 presents values of percentage of applied dose absorbed recommended for use with a soil application rate of 0.2 mg/cm^2 to 1 mg/cm^2 and an exposure duration less than or equal to 24 hours for TCDD and TCB and less than or equal to 16 hours for cadmium. No recommendations were made for BaP and DDT because the absorption fractions reported in the literature, especially when adjusted for soil loadings using Equation (6.3), covered such a wide range that the recommendations had little meaning.

Sections 6.2.1., 6.2.2. and 6.2.5. present detailed discussions of the experimental results and derivations of the values recommended in Table 6-3. Sections 6.2.3. and 6.2.4. discuss experimental data on BaP and DDT, respectively. Section 6.2.6. discusses the experimental results for benzene, toluene, and xylene, which were omitted from the analysis because the experimental conditions were too different from expected environmental conditions to allow for use in environmental risk assessment. Section 6.2.7 presents preliminary results on hexadecane.

6.2.1. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)

This section examines three studies of percutaneous absorption of TCDD applied to the skin in soil. Poiger and Schlatter (1980) and Shu et al. (1988) studied percutaneous absorption in vivo in the rat. Roy and colleagues studied percutaneous absorption in vivo in the rat and in vitro in rat and human skin (EPA, 1991; Roy et al., 1990). In Section 6.2.1.1., the experimental conditions and the results of the three studies are presented and compared. In Section 6.2.1.2., the percentages of applied dose absorbed recommended for use in risk assessment in Table 6-3 are derived.

6.2.1.1. *Experimental Results*

Poiger and Schlatter (1980) - Poiger and Schlatter (1980) investigated the percutaneous absorption of TCDD from contaminated soil. These researchers applied a paste of 67% soil and 33% water and various levels of radiolabeled TCDD to the backs of hairless rats and monitored the appearance of TCDD in the liver to determine the percentage of the applied dose that was absorbed.

Table 6-2. Dermal Absorption of Soil-Adhered Organic Compounds

Compound	Site of Application	Soil Loading (mg/cm^2)	Surface Area Exposed (cm^2)	Total Applied Dose (ng)	Concentration (ppm)	Percent Applied Dose Absorbed	Total Dose Absorbed (ng)	Exposure Period (hours)	Soil Organic Content (%)	Animal Species	Study Method	Ref.
TCDD	Back	19-25^a	3-4	350	5	2.4^a	8.4	24	NR^h	Rats	in vivo	i
	Back	19-25^a	3-4	1300	17	3.1^a	40.3	24	NR	Rats	in vivo	i
	Back	21	12	2.7^e	0.01	1.08^{b,c}	0.029	24	NR	Rats	in vivo	j
	Back	21	12	2.7^e	0.01	1.22^{b,d}	0.033	24	NR	Rats	in vivo	j
	Back	21	12	26.9^f	0.1	1.3^b	0.35	24	NR	Rats	in vivo	j
	Back	21	12	26.9^f	0.1	1.58^{b,c}	0.43	24	NR	Rats	in vivo	j
	Back	21	12	26.9^f	0.1	1.44^{b,d}	0.39	24	NR	Rats	in vivo	j
	Back	21	12	26.9^f	0.1	1.26^b	0.34	4	NR	Hairless rats	in vivo	j
	Back	21	12	26.9^f	0.1	2.02^b	0.54	24	NR	Hairless rats	in vivo	j
	Back	21	12	26.9^f	0.1	1.24^b	0.33	4	NR	Haired rats	in vivo	j
	Back	21	12	26.9^f	0.1	1.98^b	0.53	24	NR	Haired rats	in vivo	j
	Back	21	12	26.9^f	0.1	1.46^{b,q}	0.39	24	NR	Rats	in vivo	j
	Back	21	12	26.9^f	0.123	1.58^{b,r}	0.43	24	NR	Rats	in vivo	j
	Back	9-10	7	70	1	16.3^n	11.4	96	0.45	Rats	in vivo	k
	Back	9-10	1.77	17.7	1	7.7^o	1.4	96	0.45	Rats	in vitro	k
	Back	9-10	1.77	17.7	1	1.0^o	0.18	96	11.22	Rats	in vitro	k
	Breast	5-6	1.77	10.6	1	2.4^o	0.25	96	0.45	Humans	in vitro	k
BaP	Back	9	1.77	15.5	1	8.4^{o,u}	1.3	96	1.64	Rats	in vitro	l
	Back	56	1.77	100.0	1	1.3^{o,u}	1.3	96	1.64	Rats	in vitro	l
	Back	9	7	63	1	1.1^u	0.69	24	1.64	Rats	in vivo	l
	Back	9	7	63	1	3.7^u	2.3	48	1.64	Rats	in vivo	l
	Back	9	7	63	1	5.8^u	3.6	72	1.64	Rats	in vivo	l
	Back	9	7	63	1	9.2^u	5.8	96	1.64	Rats	in vivo	l

Table 6-2. (continued)

Compound	Site of Application	Soil Loading (mg/cm^2)	Surface Area Exposed (cm^2)	Total Applied Dose (ng)	Concentration (ppm)	Percent Applied Dose Absorbed	Total Dose Absorbed (ng)	Exposure Period (hours)	Soil Organic Content (%)	Animal Species	Study Method	Ref.
	Abdomen	40	12	4800	10	13.2^{g}	633.6	24	0.90	Rhesus monkeys	in vivo	m
	Abdomen	40	1	400	10	1.41^{p}	5.6	24	0.90	Humans	in vitro	m
Cadmium	Abdomen	40	1	0.52	.013	0.1	0.0005	16	0.90	Humans	in vitro	t
DDT	Abdomen	40	12	4800	10	3.3^{g}	158.4	24	0.90	Rhesus monkeys	in vivo	m
	Abdomen	40	1	400	10	1.04^{p}	4.2	24	0.90	Humans	in vitro	m
TCB	Back	9-10	7	70,000	1,000	49.7^{n}	34,860	96	0.45	Rats	in vivo	k
	Back	9-10	1.77	17,700	1,000	31.9^{o}	5,646	96	0.45	Rats	in vitro	k
	Breast	5-6	1.77	10,600	1,000	7.4^{o}	786	96	0.45	Humans	in vitro	k
	Back	9-10	1.77	17,700	1,000	9.6^{o}	1,700	96	11.22	Rats	in vitro	k

[a] Values were estimated by dividing the percentages of the applied dose in the liver after dermal application by 0.7 (fraction of the total body burden of TCDD estimated to be in the liver).

[b] Values were estimated by dividing the percentages of the applied dose in the liver after dermal application by 0.5 (fraction of the total body burden of TCDD measured in the liver).

[c] Presence of 0.5% crankcase oil as a co-contaminant.

[d] Presence of 2.0% crankcase oil as a co-contaminant.

[e] 12.5 ng/kg x assumed mean weight of rats (0.215 kg - range 180-250 g).

[f] 125 ng/kg x assumed mean weight of rats (0.215 kg - range 180-250 g).

[g] Percent absorbed = (^{14}C urinary excretion following topical application)/(^{14}C excretion following i.v. administration) x 100.

[h] Not reported.

[i] Poiger and Schlatter (1980).

[j] Shu et al. (1988).

[k] EPA (1991); Roy et al. (1990) and Driver et al. (1989).

[l] Yang et al. (1989).

[m] Wester et al. (1990a).

[n] Percentage of applied dose occurring in excreta and animal body mass as determined by a complete tissue analysis.

[o] Percentage of applied dose in the receptor fluid (using PEG-20 oleyl ether) and the skin sample following surface wash, 96 hours after topical application.

[p] Percentage of applied dose in the skin and receptor fluid following surface wash with soap and water 24 hours after topical application.

[q] TCDD added to soil in the laboratory.

[r] Environmentally contaminated Times Beach soil used in experiment.

[s] Applied as a soil/water paste (approximately ⅛ water by weight).

[t] Wester et al. (1991).

[u] Presence of 1.0% crude petroleum oil at a co-contaminant.

Table 6-3. Recommended Percentages of Applied Dose Absorbed for Soil Applications of 0.2 mg/cm^2-1.0 mg/cm^2 and Exposure Less than or Equal to 24 Hours

Chemical	Percent Absorbed
TCDD	0.1 - 3%
TCB	0.6 - 6%
Cadmium	0.1 - 1.0%

Seventy-five mg of the soil/water paste were spread over an area of 3 cm^2 to 4 cm^2. Three dose levels were used — 26, 350, and 1,300 total ng of TCDD. Soil loading rates were 19 mg/cm^2 to 25 mg/cm^2. TCDD concentrations in the soil/water paste were approximately 0.3 ppm, 5 ppm, and 17 ppm. The average percentage of dose in the liver 24 hours after dermal application was approximately 0.05% of the 26 ng dose, 1.7% of the 350 ng dose, and 2.2% of the 1,300 ng dose. Poiger and Schlatter (1980) stated that reproducible quantities of TCDD in the liver were measurable only after administration of 50 μCi or more. Since 26 ng corresponds to about 5 μCi, results for this dosage are not included in this report even though they are reported by Poiger and Schlatter (1980). Kissel and McAvoy (1989) propose that the concentration of microsomal binding protein in the liver is dose dependent. If little induction of microsomal binding occurred at the lowest dose, this would explain the low uptake of TCDD in the liver at the lowest dose.

If the percentage of total body burden is known, the percentage of applied dose absorbed can be calculated. Poiger and Schlatter noted that Fries and Marrow (1975) found 70% of the total body burden of TCDD located in the livers of female rats. Using 70% as a correction factor, the percentage of the total applied dose absorbed was 2.4% for the 350 ng dose and 3.1% for the 1,300 ng dose.

Shu et al. (1988) - Shu et al. (1988) used protocols that approximate exposure conditions experienced by humans, including exposures to TCDD in the low concentration (i.e., part per billion) range, exposure durations less than 24 hours, and exposure to TCDD in soil contaminated with waste oil. Shu et al. applied soil containing concentrations of 10 ppb and 100 ppb TCDD and from 0 - 2% oil to rats and measured the percent of applied dose appearing in the liver after 24 hours of exposure. They also measured the percent of applied dose in the liver after a 4-hour exposure period compared to a 24-hour exposure period. Finally, they measured the percent of applied dose in the liver after exposure to environmentally contaminated soil from Times Beach containing 123 ppb TCDD.

There was little difference in the percutaneous absorption of TCDD under these various conditions. The average percentages of applied dose in the liver ranged from a low of 0.54% (10 ppb TCDD, 0.5% oil, 24-hour exposure) to a high of 1.01% (100 ppb TCDD, no oil, 24-hour exposure). Shu et al. (1988) also estimated that if 100% of an orally administered dose of TCDD were absorbed, 50% of that dose would appear in the liver 24 hours after administration. Therefore, the percentages of applied dose measured in the liver after dermal application were divided by 0.5 to arrive at a total percent absorbed ranging from 1.08% to 2.02% of the applied dose.

Roy et al. (1990), EPA (1991) - Roy and colleagues applied TCDD, both neat and in soil, to rat skin in vivo and in vitro and to human skin in vitro. These investigators found that approximately 77% of a topically applied dose of 70 ng of neat TCDD was absorbed across rat skin after 96 hours. The fraction absorbed was similar whether the TCDD was studied in vivo or in vitro. Application to rat skin of 70 ng of TCDD in soil with low organic carbon content and a TCDD concentration of 1 ppm resulted in average absorption of 16.3% of the applied dose in vivo and 7.7% of the applied dose in vitro after 96 hours of exposure. Application of TCDD in a soil matrix reduced the percentage of TCDD absorbed by a factor of 5 in the in vivo test and by a factor of 10 in the in vitro test, compared to absorption of the neat compound. The average percentage of applied dose absorbed in vitro using human skin and low organic carbon soil was 2.4% after 96 hours or one-third that observed when rat skin was tested in vitro. TCDD was also applied to rat skin in vitro at a concentration of 1 ppm in a high organic carbon content soil. The average percentage of applied dose absorbed after 96 hours was 1.0%, or about one-eighth of the absorption obtained in vitro using the low organic carbon soil.

In all the in vitro experiments, samples of the receptor fluid were obtained at 1, 2, 4, 8, 24, 48, 72, and 96 hours after the beginning of the experiment. Fractions of the applied dose absorbed were calculated for each time interval. At 96 hours, samples were washed and analyzed for TCDD. The reported fraction absorbed at 96 hours includes the amount of TCDD in the sample as well as the amount in the receptor fluid.

In the in vivo experiments, urine and feces were collected and analyzed 24, 48, 72, and 96 hours after the application of the soil, and the fraction of applied dose in the urine and feces was calculated. TCDD was also administered intravenously to rats, and urine and feces were collected and analyzed. The percents of applied dose absorbed at 24, 48, 72, and 96 hours after topical application were calculated from the excreta data.

Table 6-4 shows the measured and estimated values of percent of applied dose absorbed at times from 1 to 96 hours for TCDD applied in soil with low and high organic carbon content. Some of the values in Table 6-4 are used to derive the values recommended in Section 6.2.1.2 for use in exposure assessments.

Comparison of studies - The in vivo results of Poiger and Schlatter (1980), Shu et al. (1988), and Roy and colleagues are comparable when one takes into account different vehicles, soil loading rates, and exposure durations. Poiger and Schlatter (1980) and Shu et al. (1988) used soil loading rates of about 21 mg/cm^2, while Roy et al. used loadings ranging from 6 to 10 mg/cm^2. Poiger and Schlatter used TCDD-free soils from Seveso, Italy, which were ground to a powder of homogeneous particle size and applied in a soil-water paste. Organic carbon content was unspecified. Shu et al. (1988) used TCDD-free and contaminated soils obtained from Verona and Times Beach, Missouri, with unspecified organic carbon content. In some experiments, Shu et al. (1988) added 0.5% or 2% crankcase oil to the soils. Roy et al. used a low organic carbon content (0.45%) and a high organic carbon content (11.22%) soil. Exposure durations in the Roy et al. experiments were 96 hours compared to 24 hours for the other studies. Approximate concentrations of TCDD in soil were 0.3 ppm, 5 ppm, and 17 ppm in Poiger and Schlatter (1980), 0.01 and 0.1 ppm in Shu et al. (1988), and 1 ppm in EPA (1991). Excluding the Poiger and Schlatter (1980) results for the 0.3 ppm concentration, as discussed above, and using the authors' factors for converting percent dose in liver to percent applied dose absorbed (70% and 50% of total absorbed dose assumed to be in the liver by Poiger and Schlatter [1980] and Shu et al. [1988], respectively), percents of applied dose absorbed in vivo ranged from 1.08% (Shu et al. [1988], 24-hour exposure, 10 ppb TCDD, 0.5% crankcase oil) to 16.3% (EPA [1991], 96-hour exposure, 1 ppm TCDD, low organic carbon content soil). For a 24-hour exposure period, Roy and colleagues observed 8% absorption in vivo in the rat (EPA [1991]). Given the variation in vehicles, soil application rates, and exposure durations, these in vivo results seem consistent.

Table 6-4. Absorption of TCDD Over Time

Time (hour)	LOS Rat- In Vivo[a,d]	LOS Rat- In Vitro[a,d]	LOS Human - In Vitro[b,d]	HOS - Rat In Vitro[c,d]
1	N.D.[e]	0.01 (0.01)	0.02 (0.03)	0.00
2	N.D.	0.01 (0.01)	0.08 (0.10)	0.00
4	N.D.	0.05 (0.03)	0.07 (0.05)	0.00
8	N.D.	0.16 (0.08)	0.02 (0.03)	0.00
24	8.0[f]	1.17 (0.42)	0.28 (0.14)	0.06 (0.01)
48	10.7[f]	3.53 (1.08)	0.91 (0.50)	0.27 (0.06)
72	14.8[f]	4.97 (1.36)	1.54 (0.88)	0.40 (0.06)
96	17.4[f]	6.32 (1.74)	2.25 (1.26)	0.55 (0.07)
96 (Dose in skin sample after wiping)	N.A.[g]	1.42 (0.53)	0.17 (0.11)	0.48 (0.43)
96 (Total)	16.3 (2.0)[h]	7.74 (1.34)	2.42 (1.31)	1.03 (0.44)

[a] Soil application rate = 10 mg/cm^2; LOS = Low organic content soil.

[b] Soil application rate = 6 mg/cm^2; LOS = Low organic content soil.

[c] Soil application rate = 10 mg/cm^2; HOS = High organic content soil.

[d] Numbers are the averages of the results for four or five samples. Numbers in parentheses are standard deviations.

[e] N.D. = No data.

[f] Percent absorbed estimated by dividing percent of applied dose found in the excreta at the specified time by the fraction of applied dose in the excreta at the same time after intravenous administration. The fractions of applied dose in the urine and feces after intravenous administration were 0.097 after 24 hours, 0.165 after 48 hours, 0.195 after 72 hours, and 0.212 after 96 hours. The cumulative percents of applied dose found in urine and feces after topical application of 70 ng of TCDD in low organic carbon content soil were 0.77% at 24 hours, 1.76% at 48 hours, 2.88% at 72 hours, and 3.69% at 96 hours.

[g] N.A. = Not applicable

[h] Measured total in urine, feces, and tissues.

Source: EPA (1991); Roy et al. (1990)

6.2.1.2. *Analysis of Data*

The data in EPA (1991) were used to estimate in vivo absorption in humans by adjusting experimental values to reflect differences between in vitro and in vivo test systems and between rat and human skin. Corrections were made to the data obtained after 24 hours in the in vitro system using human skin (EPA, 1991) and in the in vivo experimental systems (EPA, 1991; Shu et al., 1988; Poiger and Schlatter, 1980). Data obtained by Roy and colleagues at 96 hours rather than 24 hours after exposure were used to calculate correction factors because the amount of TCDD in the excised skin samples was measured only at 96 hours. The percent of TCDD absorbed by human skin in vitro after 24 hours was corrected by substituting data obtained for the rat after 96 hours into Equation (6.4). The ratio of absorption measured in vivo (16.3%) to that measured in vitro in rat skin (7.74%) is 2.1. The ratio of absorption in vitro in rat skin (7.74%) to absorption in vitro in human skin (2.42%) is 3.2. The ratio of absorption from low organic carbon soil in rat skin measured in vitro (7.74%) to absorption from high organic carbon soil in the same system (1.03%) is 7.5. (EPA, 1991).

In adjusting the in vitro human skin data of Roy and colleagues, it was assumed that the percentage of dose in the skin sample that could not be removed by wiping would be approximately constant between 24 and 96 hours. The mean value of the dose in the human skin sample after wiping at 96 hours was added to the dose in the receptor fluid after 24 hours to obtain an estimate of the percent of applied TCDD absorbed at 24 hours in vitro in human skin. For soils with low organic carbon content, the total percent absorbed at 24 hours was 0.45% (0.28% in the receptor fluid at 24 hours + 0.17% in the skin sample at 96 hours). This value was corrected to reflect differences in absorption measured in vivo and in vitro using Equation (6.4), producing an estimate of 0.95% (0.45% x 16.3%/7.7%) absorbed and bound to human skin in vivo after 24 hours of exposure to TCDD applied in 6 mg soil/cm^2.

Roy and colleagues tested absorption from high organic carbon content soil only in vitro in the rat (EPA, 1991). Assuming that the relationships observed in the experiment involving low organic carbon content soil apply in the case of high organic carbon content soil, the estimated absorption in vivo in humans of 0.95% was corrected for a high organic carbon content soil by applying the following equation:

$$\text{Human in vivo (ABS-HOS)} = (\text{Human in vivo ABS-LOS}) \times \frac{(\text{Species A in vitro ABS-HOS})}{(\text{Species A in vitro ABS-LOS})} \quad (6.5)$$

In Equation (6.5), LOS and HOS indicate data obtained using low and high organic carbon content soils, respectively. The estimated percent absorbed is thus 0.13% (0.95% x 1.03%/7.74%) from 6 mg/cm^2 of high organic carbon content soil.

The in vivo rat data reported in EPA (1991), Shu et al. (1988), and Poiger and Schlatter (1980) were also corrected using the EPA (1991) data and Equation (6.4). The average percent absorbed in the EPA (1991) study in vivo in the rat was 8.0%. The human absorption, estimated from Equation (6.4), is 2.5% (8.0% x 2.42%/7.74%) of TCDD applied in 10 mg soil/cm^2. The percents absorbed over 24 hours in rats, estimated from data in Shu et al. (1988) and Poiger and Schlatter (1980), ranged from 1.08% (Shu et al., 1988) to 3.1% (Poiger and Schlatter, 1980). Adjusting these data using Equation (6.4) results in an estimated human in vivo absorption ranging from 0.2% (1.08% x 2.42%/7.74%) to 1.0% (3.1% x 2.42%/7.74%) for TCDD applied in approximately 21 mg soil/cm^2.

The percents absorbed, corrected to reflect absorption in vivo in humans, range from 0.1 to 2.5%. The recommended percent of applied dose absorbed for TCDD is 0.1 to 3%. It is further recommended that assessors use the low end of this range for soils with high organic carbon content and the upper end for soils with low organic carbon content.

6.2.2. 3,3′,4,4′-Tetrachlorobiphenyl (TCB)

Roy and colleagues also studied percutaneous absorption of TCB in vivo in the rat and in vitro in rat and human skin. The protocols used in their study of TCDD, described in Section 6.2.1.1., were also used in the experiments involving TCB. Section 6.2.2.1. provides the experimental results. Section 6.2.2.2. derives the percents absorbed for use in exposure assessments that are recommended in Table 6-3.

6.2.2.1. *Experimental Results*

Application to rat skin of TCB in soil with low organic carbon content and a TCB concentration of 1,000 ppm resulted in average absorption of 49.7% of the applied dose in vivo and 31.95% of the applied dose in vitro after 96 hours of exposure. The average percentage of applied dose absorbed in vitro using human skin and low organic carbon soil was 7.36% after 96 hours or one-fourth that observed when rat skin was tested in vitro. TCB was also applied to rat skin in vitro at a concentration of 1,000 ppm in a high organic carbon content soil. The average percentage of applied dose absorbed after 96 hours was 9.64%, or about one-third of the absorption obtained in vitro using the low organic carbon soil.

In all in vitro experiments, samples of the receptor fluid were obtained 1, 2, 4, 8, 24, 48, 72, and 96 hours after the beginning of the experiment. Percents of applied dose absorbed were calculated for each time interval. At 96 hours, samples were washed and analyzed for TCB. The reported fraction absorbed at 96 hours included the amount of TCB in the sample as well as the amount in the receptor fluid.

In the in vivo experiments, urine and feces were collected and analyzed 24, 48, 72, and 96 hours after the application of the soil, and the percent of applied dose in the urine and feces was calculated. However, since the TCB was not administered intravenously to a separate group of animals, there are insufficient data to calculate percents absorbed in vivo in the rat at times less than 96 hours.

Table 6-5 shows the measured and estimated values of percent of applied dose absorbed at times from 1 to 96 hours for TCB applied in soil with low and high organic carbon content. Some of the values in Table 6-5 were used to derive the values recommended for use in exposure assessment in Section 6.2.2.2. below.

Table 6-5. Absorption of TCB Over Time

Time (hour)	LOS - Rat In Vivo[a,d]	LOS - Rat In Vitro[a,d]	LOS - Human In Vitro [b,d]	HOS - Rat In Vitro[c,d]
1	N.D.[e]	0.00	0.00	0.00
2	N.D.	0.00	0.00	0.00
4	N.D.	0.12 (0.05)	0.00	0.02 (0.03)
8	N.D.	0.72 (0.18)	0.00	0.27 (0.05)
24	N.D.	5.81 (0.48)	1.07 (0.47)	1.82 (0.33)
48	N.D.	13.79 (1.12)	3.18 (1.09)	4.34 (0.66)
72	N.D.	21.59 (1.91)	5.26 (1.78)	6.84 (0.92)
96	49.7 (10.9)[g]	29.61 (2.68)	7.10 (2.36)	8.99 (1.10)
96 (Dose in skin sample after wiping)	N.A.[f]	2.3 (0.4)	0.26 (0.06)	0.60 (0.10)
96 (Total)	49.7 (10.9)[g]	31.95 (2.58)	7.36 (2.42)	9.64 (1.13)

[a] Soil application rate = 10 mg/cm^2; LOS = Low organic content soil.

[b] Soil application rate = 6 mg/cm^2; LOS = Low organic content soil.

[c] Soil application rate = 10 mg/cm^2; HOS = High organic content soil.

[d] Numbers are averages of the results for four or five samples. Numbers in parentheses are standard deviations.

[e] N.D. = No data.

[f] N.A. = Not applicable

[g] Measured total in urine, feces, and tissues.

Source: EPA (1991)

6.2.2.2. *Analysis of Data*

The procedures described in Section 6.2.1.2. were used to adjust the experimental data to obtain an estimate of absorption of TCB in vivo in humans. Data in EPA (1991) were used to correct all experimental values to reflect differences between in vitro and in vivo test systems, between rat and human skin, and between applications of TCB in low and high organic carbon content soil. The ratio of absorption measured in vivo (49.7%) to that measured in vitro (31.95%) after 96 hours is 1.6. The ratio of absorption in vitro in rat skin (31.95%) to absorption in vitro in human skin (7.36%)

after 96 hours is 4.3. The ratio of absorption from low organic carbon content soil (31.95%) to absorption from high organic carbon content soil (9.64%) is 3.3.

It was assumed that the percentage of dose in a skin sample that could not be removed by washing would be approximately constant between 24 and 96 hours. Thus, the mean value of the dose in the skin sample for 5 samples was added to the dose in the receptor fluid at 24 hours to obtain an estimate of the fraction of applied TCB absorbed at 24 hours in vitro in human skin. For low organic carbon content soil, the total percent absorbed at 24 hours in vitro in human skin was 1.33% (1.07% in the receptor fluid at 24 hours + 0.26% in the skin sample at 96 hours). This value was adjusted using Equation (6.4) to reflect differences between absorption in vivo and in vitro in the rat, producing an estimate of 2.1% (1.33% x 49.7%/31.95%) absorbed and bound to the skin after 24 hours for TCB applied in 6 mg soil/cm^2.

Absorption from high organic carbon content soil was tested only in vitro in the rat (EPA, 1991). Equation (6.5) was used to adjust the estimated percent of TCB absorbed from low organic carbon content soil in human skin to reflect absorption from high organic carbon content soil. Assuming that the relationships observed in the experiment involving low organic carbon content soil apply in the case of high organic carbon content soil, the estimated percent absorbed is 0.63% (2.1% x 9.64%/31.95%) from 6 mg/cm^2 of soil.

Thus, the data suggest that the percent TCB absorbed from soil ranges from 0.63% for high organic content soil to 2.1% for low organic carbon. This relatively narrow range implies more precision than is appropriate considering the variability in soil characteristics and uncertain data base. EPA decided that any final recommendations for percent absorbed should span at least one order of magnitude to reflect the uncertainty. Thus, the final recommendation for percent TCB absorbed from soil is 0.6% to 6%.

6.2.3. Benzo[a]Pyrene (BaP)

The in vitro and in vivo percutaneous absorption of another highly lipophilic compound, benzo[a]pyrene (BaP), was studied by Yang et al. (1989) and by Wester et al. (1990a). Section 6.2.3.1. describes the experimental protocols used in these two studies and presents the results.

Section 6.2.3.2. provides an analysis of the results as they apply to assessment of exposure to chemicals in the environment.

6.2.3.1. *Experimental Results*

Yang et al. (1989) studied absorption of BaP from soil in rats. They used soil with an organic carbon content of 1.64%. Soil contaminated with crude petroleum oil at a concentration of 1% and with BaP at a concentration of approximately 1 ppm was applied to split thickness rat skin in a diffusion chamber, with application rates of 9 mg soil/cm^2 (described by the authors as a "monolayer") or 56 mg soil/cm^2. The average percentages of BaP absorbed after 96 hours of exposure were 8.4% and 1.3% of the initial applied dose at exposure levels of 9 mg soil/cm^2 and 56 mg soil/cm^2, respectively. The quantity of BaP absorbed, 1.3 ng, was the same regardless of the amount of soil and, hence, of BaP applied to the skin. The authors propose that the migration of BaP present in layers of soil above the "monolayer" is impeded by the extensive binding of BaP to soil particles. Yang et al. (1989) conducted a parallel in vitro study wherein BaP was applied to excised rat skin in 90 μg/cm^2 of petroleum crude oil with a BaP concentration of 100 ppm. This amounted to the same dose as that in the in vitro experiment where 9 mg/cm^2 of soil was applied. After 96 hours, 38.1% of the BaP applied in crude oil had been absorbed.

Yang et al. (1989) also applied BaP at a concentration of 1 ppm in a soil containing 1% crude petroleum oil to the backs of female rats in a monolayer (9 mg/cm^2) of contaminated soil and measured the radioactivity in excreta each day for 4 days. An experiment in which the BaP was applied in petroleum crude oil was conducted in parallel. Cumulative percentages of the soil-applied dose in excreta were 1.1% at 24 hours, 3.7% at 48 hours, and 5.8% at 72 hours. The cumulative percentage of applied dose in the excreta and tissues, that is, the percent absorbed, after 96 hours was 9.2%. Cumulative percentages of the dose from petroleum crude in excreta were 5.5% after 24 hours, 20.1% after 48 hours, 27.6% after 72 hours, and 35.3% in excreta and tissues after 96 hours. Yang et al. (1989) found no significant difference between the mean percents absorbed in the rat whether measured in vivo or in vitro. After 96 hours, the amount of BaP absorbed from petroleum crude oil was four times that of the amount absorbed from soil.

Wester et al. (1990a) studied the percutaneous absorption of BaP applied in soil and acetone in vitro using human skin and in vivo in rhesus monkeys. Soil composed of 26% sand, 26% clay, and 48% silt, containing 10 ppm ^{14}C-labeled BaP was applied to human skin samples with surface areas of 1 cm^2. The soil application rate was 40 mg/cm^2. After 24 hours, the surface of the sample was washed with soap and water. The investigators found that the BaP tended to bind to the skin in the in vitro test rather than enter the human plasma receptor phase. After 24 hours, an average of 91.2% of the BaP applied in soil was found in the surface wash, 1.4% was found in the skin, and 0.01% was found in the plasma receptor fluid. For 6 samples from 2 donors, the percents of the dose found in the skin ranged from 0.3 to 3%. For the same dose of BaP applied in acetone, an average of 53.0% of the BaP applied was found in the surface wash, 23.7% was in the skin sample, and 0.09% was in the receptor fluid.

Wester et al. (1990a) also measured in vivo percutaneous absorption in rhesus monkeys. The percentage of topically applied BaP absorbed over 24 hours averaged 13.2%. Percentages of applied dose of BaP absorbed for four subjects were 13.1%, 10.8%, 18.0%, and 11.0%. For the same dose applied in acetone the percentage absorbed over 24 hours averaged 51.0%. Percentages absorbed for each of the four subjects were 30.5%, 82.2%, 46.6%, and 44.6%.

6.2.3.2. *Analysis of Data*

Wester et al. (1990a) in vitro data for human skin are consistent with the Yang et al. (1989) in vivo data for rat skin collected at 24 hours. In Wester et al. (1990a), the percentage of applied dose in skin and fluid after 24 hours averaged 1.41%. The amount absorbed was 5.6 ng/cm^2 (40 mg soil/cm^2 x 10 ng BaP/mg soil x 0.0141). Assuming that the amount absorbed over a given time period is proportional to the concentration, the amount absorbed for a concentration of 1 ppm would be 0.56 ng/cm^2 over 24 hours. This is about six times higher than the 0.1 ng/cm^2 (9 mg soil/cm^2 x 1 ng/mg x 0.011) flux observed by Yang et al. (1989) over 24 hours in rats in vivo. Given the differences in the methods and materials used in the experiments, a sixfold difference in estimated fluxes for a 1 ppm concentration seems reasonable.

In Wester et al. (1990a), however, the average percentage of BaP absorbed from a soil loading of 40 mg/cm^2 with a concentration of 10 ppm BaP was 13.2% over 24 hours in rhesus monkeys. The amount absorbed was 53 ng/cm^2 (40 mg soil/cm^2 x 10 ng/mg x 0.132), about 9 times greater than the 5.6 ng/cm^2 (40 mg soil/cm^2 x 10 ng/mg x 0.0141) flux measured by Wester et al. (1990a) in an in vitro system using human skin. The flux measured by Wester et al. (1990a) of 53 ng/cm^2 in rhesus monkeys is equivalent to a flux of 5.3 ng/cm^2 for a concentration of 1 ppm. A flux of 5.3 ng/cm^2 is 53 times larger than the amount absorbed in rats over the same time period measured by Yang et al. (1989) for a concentration of 1 ppm.

If the percent absorbed (13.2%) obtained from the rhesus monkeys is adjusted to reflect environmental exposures to soil using Equation (6.3), the predicted absorption of BaP in 5 mg soil/cm^2 would be 100% of the applied dose. Attempts to determine an upper limit on absorption by considering data obtained from studies of neat BaP or of BaP applied in other vehicles provided little insight. Reported percutaneous absorption ranged from around 1% to over 93% of the applied dose (Kao et al., 1984, 1985, 1988; Sanders et al., 1984; Bronaugh and Stewart, 1986). Absorption was affected by, among other things, the species of the test subjects, the size of the dose, the vehicle, handling and storage of skin samples, and exposure of animals to TCDD before the experiments. Wester et al. (1990a) observed an average absorption of 53% and a maximum absorption of 82% of a dose of BaP applied to rhesus monkeys in acetone over 24 hours.

Because of the wide range of absorption fractions indicated by the data, no attempt has been made to recommend a range of values for the percutaneous absorption of BaP. Further research is required on the bioavailability of BaP in soil.

6.2.4. DDT

Wester et al. (1990a) studied percutaneous absorption of DDT in vitro in human skin and in vivo in rhesus monkeys. Section 6.2.4.1. describes the experimental protocols used in this study and presents the results. Section 6.2.4.2. provides an analysis of the results as they apply to assessment of exposure to chemicals in the environment.

6.2.4.1. *Experimental Results*

Wester et al. (1990a) studied the percutaneous absorption of DDT applied in soil and acetone in vitro using human skin and in vivo in rhesus monkeys. Soil composed of 26% sand, 26% clay, and 48% silt, containing 10 ppm ^{14}C-labeled DDT was applied to human skin samples with surface areas of 1 cm^2. The soil application rate was 40 mg/cm^2. After 24 hours, the surface of the sample was washed with soap and water. The investigators found that the DDT tended to bind to the skin rather than enter the human plasma receptor phase. After 24 hours, an average of 95.6% of the topically applied radioactivity was found in the surface wash, 1% was in the skin sample, and 0.04% was in the receptor fluid. For 6 samples from 2 donors, the percentages of the applied dose found in the skin after 24 hours ranged from 0.3 to 1.8%. For the same dose of DDT applied in acetone, an average of 63.7% was in the surface wash, 18.1% was in the skin sample, and 0.08% was in the receptor fluid 24 hours after application. The percentage of the DDT applied in acetone that was bound to the skin after 24 hours differed substantially between the 2 donors. The 3 samples from the first donor contained 7.9%, 5.0%, and 7.1% of the applied dose after the surface wash. The samples from the second donor contained 25.9%, 25.1%, and 37.8% of the applied dose.

Wester et al. (1990a) also measured in vivo percutaneous absorption in rhesus monkeys. The percentage of topically applied DDT absorbed over a 24-hour exposure period averaged 3.3%. Percentages of applied dose of DDT absorbed for three subjects were 2.7%, 3.4%, and 3.7%. When 4 monkeys received the same dose topically applied in acetone, the average percent absorbed was 18.9% and the percents absorbed for each subject were 9.2%, 30.5%, 13.8%, and 22.2%.

6.2.4.2. *Analysis of Data*

In the in vivo experiment using human skin, 1% of the applied dose of DDT was found in the skin after 24 hours and 0.04% was found in the receptor fluid, for a total of 1.04% of the applied dose absorbed over 24 hours from an application of 40 mg soil/cm^2. In rhesus monkeys, the average percentage of DDT absorbed from a soil loading of 40 mg/cm^2 with a concentration of 10 ppm DDT was 3.3%.

As noted in the discussion of BaP, the amount of soil applied by Wester et al. (1990a), 40 mg/cm^2, is large compared to the soil adherence values of 0.2 to 1.0 mg/cm^2, which are believed to be typical for environmental exposures. The extent to which these differences affect the percent of the applied dose that could be expected to be absorbed is unclear. Adjustment of the data obtained from rhesus monkeys using Equation (6.3) produces an estimated percent absorbed of about 30%.

An upper bound on absorption might be set by observing that the maximum percentage of applied dose of DDT absorbed was 37.8% in human skin samples and 30.5% in rhesus monkeys. However, because of the wide range of absorption fractions predicted by the data, no attempt has been made to recommend a range of values for the percutaneous absorption of DDT. Further research is required on the effect of soil loading on the percentage of DDT absorbed.

6.2.5. Cadmium

Wester et al. (1991) studied the percutaneous absorption of cadmium chloride from soil. Section 6.2.5.1. presents the experimental results of this study, and Section 6.2.5.2. presents a recommended absorption percentage for use in exposure assessments.

6.2.5.1. *Experimental Results*

Wester et al. (1991) studied the percutaneous absorption of cadmium chloride from water and soil. Radioactive cadmium-109 was mixed with soil (Yolo County 65-California-57-8) and applied to human cadaver skin mounted in glass diffusion cells with human plasma as the receptor fluid. Two soil application rates were used– 20 mg/cm^2 and 40 mg/cm^2. The soil was removed from the skin samples with soap and water after 16 hours of exposure. The average percentages of cadmium absorbed by samples from 2 human skin sources (3 samples from each source) were 0.08% (0.02% in the receptor fluid and 0.06% in skin) and 0.2% (0.07% in receptor fluid and 0.13% in skin) when soil was applied at 40 mg/cm^2. The average percentages absorbed from a soil application of 20 mg/cm^2 were 1.0% (0.02% in the receptor fluid and 0.08% in the skin) for each of the two sources. The average absorption from all twelve samples was 0.1%.

6.2.5.2. *Analysis of Data*

There was no difference in percentages of cadmium absorbed from soil applications of 20 and 40 mg/cm^2. To account for uncertainty which may arise from different soil types, soil loadings, concentrations, and other conditions, a range of 0.1% to 1.0% is recommended for use in exposure assessments.

6.2.6. Benzene, Toluene, and Xylene

The only published data on percutaneous absorption of volatile organic chemicals (VOCs) in soil are the studies of Skowronski et al. (1988, 1989, 1990), wherein, percutaneous absorption of benzene, toluene, and xylene was measured. The Skowronski et al. data are not presented in Table 6-2 because the conditions used in these experiments were not sufficiently similar to conditions of environmental exposure to allow use of the data in these types of exposure assessments. The measured percutaneous absorption rates may not be appropriate for use in exposure assessments for several reasons. First, the concentrations of the VOCs in soil were about 21% of the soil-VOC mixture. While such a mixture might be encountered in the environment, in general, much lower concentrations would be expected. Second, the application site was occluded during the experiment, preventing losses as a result of evaporation. In an environmental exposure to VOCs in soil, the skin would not be expected to be occluded. Third, the soil was first placed on the rat, and the VOC was subsequently added via syringe (Skowronski et al., 1990). Under these conditions, and given the high concentrations of VOCs in the mixture, the VOCs might not be mixed with and bound to the soil to the extent they would be in the environment. In Skowronski et al. (1988, 1989, 1990), the absorption from sandy and clay soils may be more representative of absorption of the neat compounds under occlusion than of soil-bound compounds encountered in the environment.

6.2.7. Hexadecane

Kissel and Duff (Kissel J.C. and Duff R. Mass transfer of soil on skin. Poster Presentation. Measuring, Understanding, and Predicting Exposure in the 21st Century. Atlanta, GA.

November 18-21, 1991) studied absorption of hexadecane applied to human skin in soil. ^{14}C-labeled hexadecane in 1.3 mg/cm^2 of soil was applied to human abdominal skin. The concentration of the hexadecane in the soil was 1,540 ppm and the total applied dose was 9,800 ng. Bulk soil organic carbon content was 3%. The soil was sieved for the experiment. The sieved fraction had not yet been assayed but is likely to have a higher organic carbon content than the bulk soil. An air inlet ring and evaporation cell were placed on top of the skin and held in place with a clamp. Throughout the experiment, air was drawn through the evaporation cell by pump and through a sorbent air trap. The soil remained on the skin for 24 hours, at which time the skin samples were washed and the skin, the receptor fluid, the solutions and swabs used to wash the sample, and the air traps were analyzed.

Losses to air accounted for the vast majority of the ^{14}C label. After 24 hours of exposure, 91% of the applied hexadecane was recovered from air traps and 8% remained in the soil. The 95% confidence interval on skin uptake includes 0 and ranged from 0 to 0.3%. EPA received this information during the final editing of this report and lacked the time to develop final recommendations for this chemical.

6.3. PREDICTIVE APPROACHES TO ESTIMATING DERMAL UPTAKE

This report has identified only nine chemicals for which percutaneous absorption from a soil matrix has been studied — TCDD, TCB, BaP, DDT, cadmium, benzene, toluene, xylene, and hexadecane. Even for these chemicals, differences between experimental conditions and exposure scenarios make it difficult to predict dermal uptake under environmental conditions. These complications and the very limited database make validation of predictive methods for untested chemicals nearly impossible.

Section 6.3.1. discusses use of the recommendations in Table 6-3 for TCDD and TCB to estimate absorption of other chlorinated dioxins, chlorinated furans, and other polychlorinated biphenyls.

Sections 6.3.2. and 6.3.3. discuss the following predictive approaches being investigated by the Agency for possible use in estimating dermal exposure to chemicals in soil:

- Determining an upper bound on percutaneous absorption using fluxes or K_p values measured for the compounds applied neat, in volatile solvents, or in other vehicles when a determination can be made that the reported absorption fraction represents a likely upper bound for absorption of the chemical from soil.

- Determining an upper bound on dermal bioavailability using data on the percentage of the dose that can be extracted under conditions more severe than would be encountered in environmental exposures.

- Using the product of the fraction absorbed of the neat compound and the fraction of the compound that is extractable from soil to produce a combined upper bound estimate of percutaneous absorption from soil.

- Using data on oral bioavailability and absorption in the gastro-intestinal tract to place an upper limit on percutaneous absorption.

- Predicting percutaneous absorption of chemicals from soil using modeling approaches based on physical chemical properties.

6.3.1. Use of Structural Analogues

Numerous chemicals are similar in structure to TCDD and TCB. The uptake measured for these chemicals may be used for the analogue chemicals, provided there is no reason to suspect that the uptake of the analogue chemicals could be significantly higher.

TCDD — Analogues of TCDD include the other polychlorinated dibenzo-*p*-dioxins (PCDDs), which differ from TCDD only in the number and location of chlorine substituents, and polychlorinated dibenzofurans (PCDFs), which differ from TCDD in having one oxygen bridge instead of two between the aromatic rings and in the number and location of the chlorine substituents. Brewster et al. (1989) studied absorption of neat TCDD applied in acetone to rats in vivo at six dosages ranging from about 12 ng to about 80 μg and three PCDFs — 2,3,7,8-tetrachlorodibenzofuran (TCDF); 1,2,3,7,8-pentachlorodibenzofuran (1-PeCDF); and 2,3,4,7,8-pentachlorodibenzofuran (4-PeCDF) — at three dosages ranging from about 8 μg to 80 μg. While the range of doses of TCDD used in Brewster et al. (1989) includes the doses used in the three soil studies, the lowest dosage of PCDFs is 100 times higher than the dose used in the Roy et al. study (EPA, 1991), 300 to 3,000 times the dosages used in Shu et al. (1988), and 5 to 20 times the dosages used in Poiger and Schlatter (1980). At the lowest dosage used for all four chemicals (8 μg), the percents of applied dose absorbed after 72 hours of exposure in the rat in vivo were 17.8% of TCDD, 48.8% of

TCDF, 25.3% of 1-PeCDF, and 34.2% of 4-PeCDF. Brewster et al. (1989) reported that the percents absorbed for TCDF and 4-PeCDF were significantly greater than the percent absorbed for TCDD. However, at the next highest dosage, 36 μg, uptakes were 19% for TCDD, 17.9% for TCDF, 8.3% for 1-PeCDF, and 24.5% for 4-PeCDF, with only the 4-PeCDF uptake exceeding the percent absorbed for TCDD. At the highest dosage, 72 μg, the uptake of TCDD was about the same as that of 4-PeCDF and higher than that of the other two PCDFs.

Roy and colleagues measured percutaneous absorption of neat TCDD both in vivo and in vitro in rats. At a dose of 70 ng, they measured absorption of about 76% of the applied dose both in vivo and in vitro. In the in vitro test, an average of 62% of the applied dose was found in the receptor fluid after 72 hours. A cumulative average of 12% of the applied dose was found in excreta of the rats 72 hours after exposure in the in vivo experiment. The percent absorbed in vivo after 72 hours was calculated to be 60% by dividing 12% by 0.195, which was the fraction of applied dose excreted within 72 hours after injection. Absorption was higher under the conditions of the experiments reported in EPA (1991) than in Brewster et al. (1989), where 40% of a comparable dose (80 ng) of TCDD was reported absorbed after 72 hours of exposure. Since on average the percutaneous absorption of neat PCDFs was similar to the absorption of neat TCDD at two of three dose levels in Brewster et al. (1989) and since the conditions of the experiments reported in EPA (1991) resulted in higher absorption fractions at the same dose levels, use of the upper bound (3%) in Table 6-3 is recommended as sufficiently conservative for use in assessments of other polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans.

PCBs — Analogues of TCB include the other polychlorinated biphenyls (PCBs), which differ only in the number and location of the chlorine substituents. Samples from contaminated waste sites are often analyzed for Aroclors, which are commercial mixtures of PCB isomers, widely used before 1991 as lubricants, hydraulic fluids, heat transfer fluids, and dielectric fluids in applications where fire retardant fluids were required. Aroclors are mixtures of PCBs containing 1 to 10 chlorines.

Data exist on absorption of neat hexachlorobiphenyl and on neat Aroclor mixtures containing 42% and 54% chlorine by weight. Shah et al. (1987) studied absorption of neat 2,4,5,2′,4′,5′-hexachlorobiphenyl in vivo in adult and young rats. At a dose of 16 $\mu g/cm^2$, 33.5% of the dose was absorbed in the adult rat and 40.7% of the dose was absorbed in the young rat after 72 hours. Wester et al. (1990b) studied percutaneous absorption of the PCB commercial mixtures, Aroclor 1242 and 1254, containing 42% and 54% chlorine by weight, respectively, in vivo in rhesus monkeys. The compounds were applied in mineral oil and trichlorobenzene solvents at doses between 4.0 and 4.8 $\mu g/cm^2$. After 24 hours, the application site was washed with soap and water. Urine and feces were collected daily for 30 days. Average dermal absorption of Aroclor 1242 was 20.4% from mineral oil and 18.0% from trichlorobenzene. Average absorption of Aroclor 1254 was 20.8% from mineral oil and 14.6% from trichlorobenzene.

In the Roy et al. study (EPA, 1991), 49.7% of a dose of 70 μg of TCB applied in low organic carbon content soil was percutaneously absorbed after 96 hours in vivo in the rat. This absorption rate is comparable to the average rates measured in Shah et al. (1987) in rats over 72 hours for neat hexachlorobiphenyl – 33.5% in the young rat and 40.7% in the adult rat. The uptakes of Aroclors 1242 and 1254 from mineral oil and triclorobenzene solvents in rhesus monkeys measured by Wester et al. (1990b) are consistent with the uptake of hexachlorobiphenyl in the rat (averages of 14.6% to 20.8% for a 24-hour exposure for monkeys and 33% to 41% for a 72-hour exposure for rats). Uptake of TCB (49.7% of a dose in soil over 96 hours in the rat) reported in EPA (1991) appears to equal or exceed uptake of similar PCBs. Therefore, it is appropriate to apply the recommendations for TCB in Table 6-3 to all PCBs and Aroclors. The upper bound of 6% should be used.

6.3.2. Upper Bounding Estimates of Dermal Bioavailability and Percutaneous Absorption

To be absorbed from soil, a chemical must be bioavailable. To be bioavailable via the dermal route, the chemical must desorb from the soil and come into contact with the absorption barrier, that is, the skin. Depending on the amount of soil applied, a large percentage of the applied dose may have to diffuse through the soil layer before reaching the skin. Volatilization, friction, and washing may remove some fraction of the applied dose before it can reach the absorption barrier. The mechanisms described in Chapter 2 govern absorption of chemicals in contact with the skin. In the previously described studies of dermal absorption of chemicals from soil, all processes affecting absorption, such as desorption from soil, diffusion through soil, evaporation, solubilization in sweat or oils, and diffusion across the stratum corneum are represented in the results, which are typically reported as the percentage of applied dose absorbed. When absorption of a chemical from soil has not been studied, it may be possible to use data from other sources to place upper bounds on one or more of the factors affecting dermal absorption from soil and to calculate an upper bound on such absorption. This Section discusses several types of data that may be useful in calculating upper bounds on percutaneous absorption from soil.

6.3.2.1. *Data on Absorption from Other Vehicles*

In many cases, percutaneous absorption of the neat compound will have been studied when data on absorption of the chemical applied in soil are not available. In these types of studies the chemical is usually applied in a solvent, such as acetone, which evaporates, leaving behind the pure compound. In such a study, the compound can usually be considered to be completely bioavailable in the sense that it is unbound to a vehicle and is in contact with the absorption barrier (i.e., the skin). Thus, the fraction of the neat compound that is absorbed may represent an upper bound on the fraction absorbed from soil, where the chemical may be bound to some extent to the soil and where all of the chemical may not be immediately in contact with the skin surface.

The assumption of complete bioavailability raises some issues that must be investigated. The assumption is probably more appropriate for low volatility compounds. For volatile chemicals, volatilization and percutaneous absorption will be competing processes. In studies of the neat compound where the skin is not occluded, most of a VOC will probably volatilize before absorption can occur. In soil, however, the fraction of the VOC in contact with the skin may be partially occluded by outer layers of soils particles, slowing evaporation and increasing the fraction of the VOC available for absorption over the exposure period (for example, see the modeling analysis of absorption of benzene from soil in Burmaster and Maxwell [1991], where the predicted percentage of applied dose absorbed increases with increasing soil loadings). Thus, there is a possibility that using data from a study of a neat VOC may not be an upper bound on the percentage that could be absorbed from soil.

In addition, caution must be used when the applied doses of the neat compound are not of the same order of magnitude as the environmental doses in the exposure scenario. If the experimental applied dose per unit area is much larger than the applied dose predicted by the exposure scenario, which may often be the case, it may be more appropriate to use the total amount of compound absorbed rather than the percent of applied dose absorbed in the exposure assessment. For example, if the neat applied dose were 4 $\mu g/cm^2$, and the percent of applied dose absorbed were 5% over 24 hours, the experimentally determined absorbed dose would be 200 ng/cm^2. If the applied dose in the exposure scenario is 1 $\mu g/cm^2$, however, multiplying the applied dose by 5% produces an uptake for the exposure scenario of only 50 ng/cm^2, compared to 200 ng/cm^2 for the neat compound. In this case, it would be more appropriate to assume an absorbed dose of 200 ng/cm^2 for the exposure scenario based on uptake of the neat compound, equal to absorption of 20% of the applied dose, rather than 5% of the applied dose. A mass balance should always be done to ensure that the total applied dose in the exposure scenario is greater than or equal to the calculated absorbed dose.

In studies of absorption of neat compounds, a small amount of the chemical is usually applied in a solvent such as acetone, which dissolves leaving the pure chemical on the skin (e.g., Wester et al., 1990a). In some cases, percentages absorbed of the chemical applied in some other vehicle such as an oil (e.g., Yang et al., 1989) or a small amount of water (e.g., Skog and Wahlberg, 1964) may be available. Use of such data to estimate absorption from soil may be appropriate provided a determination can be made that the fraction absorbed from the other vehicle represents a likely upper bound on the fraction which could be absorbed from soil. In addition to the issue of disparities between experimental and environmental doses, the question of the dermal bioavailability of classes of chemicals in various vehicles relative to bioavailability of the compound in soil should be considered.

All of the issues discussed in Section 6.1. relating to differences between in vivo and in vitro results and between results obtained using different species also apply to this type of data.

6.3.2.2. *Soil Extraction Data*

The percentage of a chemical that can be extracted from soil under conditions more severe than those encountered at the skin surface will place an upper bound on the absorption of the chemical. If complete absorption of the extracted material is assumed, the percentage of the chemical extracted from the soil can be used as a surrogate for the percentage of applied dose absorbed.

For example, for sites covered by RCRA, the Agency uses an extraction method to estimate the extent of natural leaching of metals from soils. The TCLP method (55 FR 11798) and its predecessor, the EP-Tox method (46 FR 35247), call for 24-hour extractions of soil with weak acid. EPA has begun investigating the feasibility of using such data to set upper bounds on bioavailability of metals from soil. Issues that will be addressed include a comparison of the efficiency of the extraction methods to the potential extraction efficiency of conditions encountered on the skin, appropriate extraction procedures for different classes of chemicals, the effect of soil properties on extraction efficiency, and the effect of contaminant concentration on extraction efficiency.

6.3.2.3. *Combined Upper Bounding Estimate*

If upper bounding estimates are available for both bioavailability (Section 6.3.2.1.) and percutaneous absorption (Section 6.3.2.2.), the product of the fraction of the chemical in soil which is extractable and the upper bound on the fraction absorbed will provide an upper bounding estimate of absorption of the chemical from soil.

6.3.2.4. *Data on Oral Bioavailability*

The Agency is investigating the use of absorption fractions for chemicals in the gastrointestinal tract as upper bounding estimates for absorption via the dermal route. Such absorption fractions, sometimes referred to as oral bioavailabilities, are often available for chemicals administered in a variety of vehicles, including feed, water, and occasionally soil. When chemicals are administered in solid vehicles such as feed and soil, oral absorption fractions provide a combined estimate of the fraction of an administered dose that is extracted from the vehicle and subsequently absorbed. Absorption is generally believed to be greater via the oral route than via the dermal route.

Some issues need to be resolved in order to confidently use such data as upper estimates of bioavailability. If the chemical is administered in a vehicle other than soil, the affinity of the chemical for the vehicle may reduce absorption in the G-I tract. Some studies report the fraction of the chemical excreted in feces as a measure of material that is not absorbed. However, since some chemicals are excreted in feces after absorption, the assumption that the fraction of the dose that is not in the feces was absorbed produces a minimum estimate rather than an upper bounding estimate of oral absorption.

6.3.3. Theoretical Modeling of Percutaneous Absorption from Soil

The Agency is investigating methods for estimating percutaneous absorption of chemicals from soil. Because so few studies of absorption of chemicals from soil are available, the models described below have had only minimal testing. Although these models cannot yet be considered validated, they provide a promising approach to estimating compound-specific percutaneous absorption values (i.e., percent of applied dose absorbed or amount absorbed during a specified exposure duration) for organic soil pollutants.

In Section 4.4., a procedure is outlined for deriving K_p values for various media. As indicated in Equation (4.32), $K_{p,s}^{soil}$ can be estimated from an aqueous $K_{p,s}^{w}$ as follows:

$$K_{p,s}^{soil} = \frac{K_{p,s}^{w}}{K_{soil/w}} \tag{6.6}$$

where:

$K_{p,s}^{soil}$ = Skin permeability coefficient for chemicals in soil (cm/hr)
$K_{p,s}^{w}$ = Skin permeability coefficient for chemicals in water (cm/hr)
$K_{soil/w}$ = Soil/water partition coefficient (unitless)
= $K_D \rho_{soil}$ (10^{-3} kg/g) (10^{3} cm^3/L)

where:

K_D = Soil/water partition coefficient (L/kg)
ρ_{soil} = Density of soil (g soil/cm^3 soil)

It follows that the steady-state dermal flux into skin from the soil can then be calculated as:

$$J_{ss} = C_{soil}\, \rho_{soil}\, K_{p,s}^{soil} \tag{6.7}$$

where:

J_{ss} = Flux (mg/cm^2-hour)

C_{soil} = Contaminant concentration in soil (mg/kg) (10^{-3} kg/g)

This model assumes that partitioning between soil and interstitial water is the dominant process by which the chemical is made available for absorption. In reality, the contaminant is likely to partition into the interstitial air and oily phases (present in the soil-skin system) and contact the skin directly from these phases as well. To the extent that these mechanisms are of lesser importance, they may be ignored for this first approximation.

A preliminary analysis was conducted to see how well Equation (6.7) predicts the flux rates measured in the experiments reported in EPA (1991), Roy et al. (1990) and Yang et al. (1989) on TCDD, TCB, and BaP. It was assumed that C_{soil} would remain constant over the course of the experiment. The analysis showed that the predicted fluxes exceeded the measured values, especially as the duration of the experiment increased. In some cases the predicted flux values resulted in estimates of the absorbed dose which exceeded the applied dose because Equation (6.7) does not account for removal of the contaminant over time (reduction in source strength) due to losses from volatilization and absorption into the skin.

Therefore, a simple model was constructed which maintains the mass balance of the contaminant as reductions in the concentration caused by dermal absorption and volatilization occur. The following expression can be derived for contaminant concentration in soil as a function of time:

$$C_{soil} = C_{soil}^{o}\, e^{-(k_{soil} + k_{vol})\, t} \tag{6.8}$$

where:

C^o_{soil} = Initial contaminant concentration in soil on skin (mg/kg) (10^{-6} kg/mg)

k_{soil} = $K^{soil}_{p,s}\ \rho_{soil}$ 1000 / AF (hour^{-1})

k_{vol} = $K_h\ D_{air}$ 3600/(AF K_D l) (hour^{-1})

t = Time (hour)

and,

AF = Soil to skin adherence factor (mg/cm^2-hour)

K_h = Dimensionless Henry's law constant

D_{air} = Molecular diffusivity in air (cm^2/sec)

l = Thickness of boundary layer at air-soil interface (cm)

Assuming Fick's first law applies over the duration of soil contact, the flux (J, mg/cm^2-hour) at any time t can be estimated as:

$$J = C_{soil}\ \rho_{soil}\ K_p^{soil} = C^o_{soil}\ \rho_{soil}\ K_p^{soil}\ e^{-(k_{soil} + k_{vol})t} \tag{6.9}$$

The absorbed dose per event (DA_{event}, mg/event) can then be calculated by integrating the flux over time and multiplying by the area of skin exposed, yielding:

$$DA_{event} = \frac{A\ C^o_{soil}\ \rho_{soil}\ K_p^{soil}}{k_{soil} + k_{vol}}[1 - e^{-(k_{soil} + k_{vol})\ t_{event}}] \tag{6.10}$$

where:

A = Skin surface area available for contact (cm^2)

t_{event} = Duration of exposure event (hour)

Finally the absorption fraction (ABS) is calculated as the absorbed dose divided by the applied dose, yielding:

$$ABS = \frac{\rho_{soil}\, K_{p,s}^{soil}}{AF\ (k_{soil} + k_{vol})} \left[1 - e^{-(k_{soil} + k_{vol})\, t_{event}}\right] \tag{6.11}$$

The permeability coefficient and soil adherence factor are discussed elsewhere in this document. The remaining parameters needed for Equations (6.10) and (6.11) are discussed below:

- Boundary Layer Thickness - This is the unmixed layer of air over the skin through which chemicals move by molecular diffusion. The thickness will vary depending on the velocity of air currents in the bulk air stream and the surface configuration and orientation. McKone (1990) selected of value of 0.5 cm, which may be used in the absence of other information.

- Soil Density - This is the bulk density of the soil and is typically about 1.35 g/cm^3.

- Air Diffusivity - This is a chemical specific value which reflects the propensity of a chemical to diffuse through the air. Measured values for a number of chemicals are available (e.g., see Thibodeaux, 1979). Lacking data, extrapolations can be made from a known value for one chemical to another on the basis of molecular weight:

$$D_{air-a} = D_{air-b} \left[\frac{MW_b}{MW_a}\right]^{0.5} \tag{6.12}$$

  Subscripts a and b refer to chemical a and chemical b.

- Contact Time - This is the time that soil remains in contact with the skin. As discussed in Chapter 8, no data are available for this parameter, but it probably corresponds roughly to the time between washings. Accordingly, it probably varies from a few hours to 24 hours. A central estimate of 12 hours is recommended for default purposes.

- Henry's law constant - This is a chemical specific value which represents the equilibrium partitioning of a chemical between water and air. Measured values for a number of chemicals are available in chemical property handbooks such as Lyman et al. (1982). The Henry's law constant (H) can be calculated in units of pressure-volume/moles as the ratio of the vapor pressure to the aqueous solubility of a chemical. K_h is the dimensionless form of the Henry's law constant, H, calculated as follows:

$$K_h = \frac{H}{RT} \tag{6.13}$$

where:

H = Henry's law constant (vapor pressure [atm]/water solubility [mol/m^3])
R = The ideal gas constant (8.205 x 10^{-5} m^3-atm/mol-°K)
T = Ambient temperature (°K)

A similar approach for estimating the dermal absorption of compounds from a soil matrix has been described by McKone (1990). This approach is based on a fugacity model proposed by Kissel and McAvoy (1989) that uses the physical-chemical properties of the compound and the soil to estimate transport across the combined soil and skin layer, taking evaporation into account. The Kissel and McAvoy model is linked to a physiologically based pharmacokinetic model which accounts for blood flows, excretion, and metabolism.

The model calculates the fraction of chemical taken up by the dermal route as a function of an overall mass transfer coefficient from soil through the combined soil and skin layer, an overall mass transfer coefficient from soil through the combined soil and air boundary layer, the concentration of the chemical in the soil, the amount of soil deposited on the skin, and the length of the exposure period. The overall mass transfer coefficients are estimated from the diffusivities of the chemical in air, soil, and skin. The diffusion coefficients for skin and soil are estimated from the fugacity capacities of air, water, and soil, and from diffusivities of the chemical in air and water. In this analysis, the skin is treated as a mixture of solid phases and water, and diffusion through the solid particles is assumed to be negligible compared to diffusion through the water phase.

Fugacity, which has units of pressure, represents the escaping tendency of a chemical from a phase. When a system is in equilibrium, the fugacities of all phases are equal. Concentrations are related to fugacities as follows:

$$C = Z \, x \, f_z \tag{6.14}$$

C = Concentration of chemical in soil, water, skin, etc. (mol/m^3)

Z = Fugacity capacity (mol/m^3-atm)

f_z = Fugacity (atm)

The fugacity capacities of three environmental compartments -- soil, water, and air -- can be estimated as follows (Mackay and Paterson, 1981, 1982):

$$Z_{soil} = \frac{\rho_{soil} K_D}{H} x \frac{10^3\ cm^3}{1\ L} x \frac{10^{-3} kg}{1g} \quad (6.15)$$

$$Z_{water} = \frac{1}{H} \quad (6.16)$$

$$Z_{air} = \frac{1}{RT} \quad (6.17)$$

Using the McKone model, Burmaster and Maxwell (1991) estimated the uptake of benzene, naphthalene, phenanthrene, fluoranthene, benzo[a]pyrene, and indeno(1,2,3-cd)pyrene for a 12-hour exposure duration as a function of the amount of soil deposited on the skin.

For BaP, the one compound of the six for which data on dermal uptake from soil are available, the McKone (1990) model estimated 99% uptake for a loading of 0.1 mg soil/cm^2, about 55% uptake for 1 mg soil/cm^2, about 2% for 10 mg soil/cm^2, and less than 1% for 32 mg soil/cm^2 over 12 hours. Yang et al. (1989) in comparison measured a 1.1% uptake of BaP in vivo in the rat after 24 hours and 9.2% uptake after 96 hours for a 9 mg soil/cm^2 loading. Yang et al. (1989) also measured a 1.3% uptake in vitro for a 56 mg soil/cm^2 loading after 96 hours and 8.4% uptake from 9 mg soil/cm^2 after 96 hours. The Agency is still in the process of testing the model described by Equation (6.10). The results from Burmaster and Maxwell (1991) seem consistent with experimental data in the rat and in human skin in vitro. However, Wester et al. (1990a) measured an average uptake of 13.2% from a 40 mg/cm^2 soil loading after 24 hours of exposure in rhesus monkeys, a much higher absorption than that predicted by the models, the Yang et al. (1989) results in the rat, and the Wester et al. (1990a) results using human skin in vitro.

For indeno(1,2,3-cd)pyrene, Burmaster and Maxwell (1991) estimated about 97% uptake over 12 hours for a soil loading of 0.1 mg/cm^2, about 25% uptake for a loading of 1 mg/cm^2, and 1% uptake for a loading of 10 mg/cm^2. For fluoranthene, they estimated about 90% uptake for loadings between 0.1 and 3 mg/cm^2, a 40% uptake for a loading of 10 mg/cm^2, about 8% uptake for a loading of 32 mg/cm^2, and less than 1% at 100 mg/cm^2. For naphthalene, they predicted about 10% uptake for soil loadings between 0.1 and 3 mg/cm^2, increasing to about 30% uptake at a loading of 100 mg/cm^2. The model predicts that uptake of benzene is about 1% to 2% for loadings of 0.1 to 10 mg/cm^2 and increases to about 8% for a loading of 100 mg/cm^2.

Burmaster and Maxwell concluded that uptake fraction is a strong, nonlinear function of the number of rings and recognized the octanol-water partition coefficient ($K_{o/w}$) and the dimensionless Henry's law constant (K_h) as physico-chemical properties that can be used to predict the uptake fraction.

McKone (1990) observed that there are few data on dermal uptake of chemicals from a soil matrix with which to test the model. However, he drew several generalizations from a theoretical analysis of dermal uptake of chemicals from soil. He observed that dermal uptake is influenced strongly by the soil loading on the surface of the skin, the octanol/water partition coefficient, $K_{o/w}$, and the dimensionless Henry's Law Constant, K_h, of the penetrant. $K_{o/w}$, as discussed in Chapter 4, is a unitless partition coefficient and represents the ratio of the concentration of the penetrant in octanol to the concentration of the penetrant in water under equilibrium conditions.

McKone (1990) drew further generalizations by running his model using a variety of chemical properties and soil adherence values similar to the 0.2 to 1 mg/cm^2 range discussed in Chapter 8. First, he concluded that for organic compounds with a $K_{o/w}$ of 10^6 or less and a dimensionless Henry's law constant (K_h) less than 0.001, it is not unreasonable to assume 100% uptake in 12 hours. Second, for compounds with a K_h of 0.01 and above, the uptake fraction is unlikely to ever exceed 40% in 12 hours and should be well below this when $K_{o/w}$ is greater than 10. Third, for compounds with a K_h of 0.1 and above, no more than 3% uptake in 12 hours should be expected. None of these generalizations would apply to metals and inorganic compounds. EPA is evaluating the reasonableness of these generalizations.

6.4. ESTIMATION OF DERMALLY ABSORBED DOSE

The first step in estimating DA_{event} is to identify an appropriate absorption fraction for the compounds of interest. First priority is given to values determined experimentally. If such data are not available, then predictive procedures must be used.

Once the absorption fraction (ABS) is established, it is used to estimate the absorbed dose per event (DA_{event}) as follows:

$$DA_{event} = C_{soil}\ AF\ ABS \tag{6.18}$$

where:

DA_{event} = Absorbed dose per event (mg/cm^2-event)
C_{soil} = Contaminant concentration in soil (mg/kg)(10^{-6} kg/mg)
AF = Adherence factor of soil to skin (mg/cm^2-event)
ABS = Absorption fraction

As discussed in Section 6.3.3., theoretical models that estimate DA_{event} on the basis of a soil permeability coefficient (see Equation [6.10]) rather than ABS are being investigated. This approach offers some advantages in that the $K_{p,s}{}^{soil}$ should remain constant over a wider range of conditions, such as the amount of soil on the skin and the concentration of the chemical in the soil. This approach is also better suited to considering nonsteady-state conditions than ABS. However, since these procedures are not as well developed, it is currently recommended that the users first consider the ABS procedures for estimating dose.

7. DERMAL ABSORPTION OF CHEMICAL VAPORS

A discussion of absorption of chemicals from the air completes the triad of the major media (others being soil and water) from which the entry of chemicals through the skin is possible. Like absorption of chemicals from water, vapor absorption through the skin requires that the chemical first be capable of achieving a sufficient concentration in the media to provide a significant driving force for skin penetration. Many chemicals, due to their low vapor pressure, cannot achieve adequate vapor concentration to pose a dermal exposure hazard. For chemicals that can achieve adequate vapor concentrations, it has been assumed that they are primarily absorbed by the respiratory tract (in the absence of respiratory protection). However, vapor absorption of chemicals through the skin has been demonstrated by a number of researchers (Hanke et al., 1961; Dutkiewicz and Piotrowski, 1961; Piotrowski, 1967, 1971; Hefner et al., 1975; Riihimaki and Pfaffli, 1978; Wieczorek, 1985; McDougal et al., 1986, 1987, 1990; Clewell et al., 1988; Tsuruta, 1989). Because of the large surface area of the skin, compounds with even small flux values may be extensively absorbed across the skin and result in a systemic chemical burden. The potential for significant contribution to the absorbed dose by dermal exposure to chemical vapors is important to consider, particularly in situations where respiratory protection is provided.

Most of the studies of vapor absorption have addressed the amount of chemical that is actually absorbed through the skin with potential to cause systemic effects. It is also important to consider whether the presence of a chemical in the skin can damage the barrier function of the skin, cause irritant effects, or cause skin sensitization. Most methods for determining fluxes or permeability constants focus only on the amount of chemical that is absorbed through the skin. These methods may underestimate the amount of chemical that is actually absorbed and may give no information about the concentration of the chemical in the skin that may cause local effects.

Dermal absorption of chemical vapors has significant similarities and differences with the absorption of chemicals from water and soil. Human exposures to chemicals in the air are most often considered to be at a constant concentration due to the large volume of contaminant-containing air in most occupational or environmental situations. Most laboratory studies designed to measure the rate of absorption or determine the permeability constant also use constant concentrations of chemicals. In the case of absorption of chemicals from water, human exposures during bathing or swimming probably involve a constant concentration again due to the large volume of water. Most laboratory studies attempt to maintain a constant concentration of chemical in aqueous solutions to investigate fluxes or penetration rates. In the case of dermal exposure to soil, people are probably exposed to a finite amount of chemicals in the soil. The mobility of chemicals in soil is assumed to be much less than the mobility of chemicals in water and air. Most laboratory studies addressing the absorption of chemicals from soil use a finite dose, and the percent absorbed of that finite dose as the measure of absorption. The mobility of a chemical in the soil is a complex process that is poorly understood and is complicated by the fact that soil is a very heterogeneous media that is different in various parts of the country, but air can be safely assumed to be the same in different parts of the country. For these reasons, properly conducted laboratory experiments regarding the absorption of chemicals from air may be more easily applied to the human exposure situation than absorption of chemicals from other media.

The state of hydration of the skin has been shown to affect the penetration of chemicals (see Chapter 2). For chemicals absorbed from water, the presence of the water itself may alter the penetration rates by causing the water content of the skin to change. Chemicals from the soil may also affect the water composition in the skin either by causing occlusion which would increase the water content, or by dehydrating the skin by absorbing water. For chemicals in the air, the effect of the air on the permeability process is minimal compared to the effects of soil and water. The effect of protective clothing, skin temperature, and exercise on dermal penetration is an important consideration for chemical vapor exposures as they are for soil exposures. These considerations should be taken into account for risk assessments.

Due to time constraints, the new procedures for estimating the dermal dose during nonsteady-state conditions have not been incorporated into this Chapter. Hopefully these procedures can be developed for dermal exposure to vapors in follow-up efforts.

7.1. FACTORS AFFECTING THE DERMAL ABSORPTION OF VAPORS

There are many factors that can affect the dermal absorption of vapors and gases. It is most useful to categorize these factors as chemical characteristics, chemical-biological parameters, and exposure parameters that can affect the penetration process. Many of these factors affect the absorption of chemicals regardless of the exposure media. In fact, these factors would be all that are necessary to explain absorption from these media if we totally understood the concepts and if the parameters were fully characterized.

7.1.1. Chemical Characteristics

The physical characteristics of a chemical are key determinants of its permeability. Characteristics such as molecular weight, molecular size, molecular charge, and polarity provide information about a chemical that can be used to provide some general guidelines about the diffusion of a chemical either in gas, fluid, or solid media. Increasing each of these parameters generally decreases the diffusion of a chemical. These characteristics are primarily responsible for the solubility in water, the capacity of soil and air (volatility), and the form of a chemical at any given temperature.

The physical form of the chemical, i.e., liquid or vapor, will affect the concentration of the compound at the skin surface, but should not affect the solubility of the compound in the skin unless damage occurs to the stratum corneum from interaction with the chemical (Scheuplein and Blank, 1971; McDougal et al., 1990).

Theoretically, knowledge of all of the chemical species involved in a chemical reaction, the reaction rates of the reactants and the products, is needed to characterize a system for modeling or dosimetric adjustment purposes. In practice, however, complete information is usually not available. The degree to which such parameters need to be characterized depends on the toxicity endpoint of interest or the "dose" of interest. For example, if the dermal layer is the target tissue, then parameters for the reactions in the epidermis and dermis may be necessary. In contrast, modeling for toxicity remote to the skin may not require sophisticated modeling of the portal-of-entry. Similar dosimetric distinctions and ranges of refinement for predicting "dose" have been characterized for the inhalation route (Jarabek et al., 1990; Dahl, 1990; EPA, 1990c). General classification (stable, reactive, metabolizable, and transition) schemes to characterize compounds have been developed to reduce the complexities of the above considerations using calculations of free energy reactions and approximation techniques for time and spatial dependencies (Dahl, 1990; Overton and Miller, 1988).

absorption of chemicals regardless of the exposure media. In fact, these factors would be all that are necessary to explain absorption from these media if we totally understood the concepts and if the parameters were fully characterized.

7.1.1. Chemical Characteristics

The physical characteristics of a chemical are key determinants of its permeability. Characteristics such as molecular weight, molecular size, molecular charge, and polarity provide information about a chemical that can be used to provide some general guidelines about the diffusion of a chemical either in gas, fluid, or solid media. Increasing each of these parameters generally decreases the diffusion of a chemical. These characteristics are primarily responsible for the solubility in water, the capacity of soil and air (volatility), and the form of a chemical at any given temperature.

The physical form of the chemical, i.e., liquid or vapor, will affect the concentration of the compound at the skin surface, but should not affect the solubility of the compound in the skin unless damage occurs to the stratum corneum from interaction with the chemical (Scheuplein and Blank, 1971; McDougal et al., 1990).

Theoretically, knowledge of all of the chemical species involved in a chemical reaction, the reaction rates of the reactants and the products, is needed to characterize a system for modeling or dosimetric adjustment purposes. In practice, however, complete information is usually not available. The degree to which such parameters need to be characterized depends on the toxicity endpoint of interest or the "dose" of interest. For example, if the dermal layer is the target tissue, then parameters for the reactions in the epidermis and dermis may be necessary. In contrast, modeling for toxicity remote to the skin may not require sophisticated modeling of the portal-of-entry. Similar dosimetric distinctions and ranges of refinement for predicting "dose" have been characterized for the inhalation route (Jarabek et al., 1990; Dahl, 1990; EPA, 1990c). General classification (stable, reactive, metabolizable, and transition) schemes to characterize compounds have been developed to reduce the complexities of the above considerations using calculations of free energy reactions and approximation techniques for time and spatial dependencies (Dahl, 1990; Overton and Miller, 1988).

Similar schemes could be applied to characterize compounds with respect to potential for interaction with the skin.

7.1.2. Chemical-Biological Parameters

This is a category of parameters that are defined only with respect to interaction of the chemical with the biological system. Partition coefficients (a solubility parameter), binding, and metabolism are chemical parameters measured with respect to a specific biological system. These measures of interaction can have an effect on both the amount of chemical available in the skin and the amount of chemical that can enter systemic circulation. A partition coefficient is the ratio of concentrations in adjacent media that would be achieved if equilibrium occurred. Partition coefficients may be determined for the skin and another vehicle such as water or air, or using some media as a surrogate for the skin such as oil or octanol. According to the definition, chemicals that have a greater partition coefficient for the skin will generally achieve higher concentrations in the skin and, as a result, will also appear in systemic circulation to a greater extent than chemicals that have lower partition coefficients. However, the partition coefficient between the skin and blood is the ultimate determinant of the amount of chemical that will appear in the blood, and therefore, this is the best partition coefficient parameter.

Similar to compounds in the neat form or in an aqueous vehicle, the rate of dermal permeation of a selected group of organic vapors is highly correlated with their lipid solubility. McDougal et al. (1990) demonstrated that a general trend between fat/air partition coefficients and K_p values exists in the rat. For example, styrene vapor, with a fat/air partition coefficient approximately seven times greater than that of benzene, penetrates rat skin about eleven times greater than benzene. As shown in Equation 7.2 (presented later in this chapter) this relationship should prove useful for making estimates of permeability based on fat/air partitions in the absence of experimental permeability constants.

Covalent or very slowly reversible binding in the stratum corneum, epidermis, or dermis may increase the amount of chemical in the skin and reduce the amount of chemical that enters systemic circulation depending on the relationship between available concentration for penetration and the binding capacity of the skin. Conversely, if the reaction products are toxic, then reactions within various skin layers would increase the delivery of toxic molecules to the tissue. Thus, irritancy or corrosiveness within the skin may be increased or decreased depending on whether it is the bound or free chemical that causes the effect. A chemical that undergoes metabolism in the skin may achieve a lower concentration in the skin than a chemical that is not metabolized, provided that the rate of metabolism is significantly large compared to the rate of entry into the skin. Similarly, the amount of parent chemical that enters systemic circulation may be reduced by metabolism in the skin.

7.1.3. Biological Parameters

Characteristics of the skin which can differ between species and at different body sites within the same species can affect the dermal absorption of vapors, just as they affect penetration from other media. The important parameters are most likely: amount and composition of lipids on the skin surface, hair follicle and sebaceous gland density, thickness and composition (including hydration) of each layer of the skin, rate of blood flow to the skin, and metabolic rate in the skin (see Chapter 2). To date, there is no information to suggest that morphological differences have any different effects on penetration from water, soil, or air.

7.1.4. Exposure Parameters

Several parameters that affect penetration of a chemical into the skin can be controlled, in contrast to either the chemical characteristics or the chemical-biological parameters. These exposure parameters are: concentration available to the skin, skin surface area exposed, condition of the skin, and loss of chemical from the skin by evaporation after exposure.

One factor widely recognized to affect the dermal absorption rate is the concentration of the compound in the vehicle, including air or donor solution (Chapter 2). The primary difference between a pure liquid and the vapor phase of the compound, relative to dermal permeation, is the concentration difference between these states. The pure liquid form is far more concentrated than the vapor form. As a result, the flux of the pure liquid form is expected to be greater than that of the compound in the vapor phase. The results of Barry et al. (1985) support this hypothesis. In experimental studies the concentration may be constant or capable of being depleted by absorption but, in either case, must be carefully controlled and quantitated to allow the study to be predictive.

Surface area exposed is another parameter that must be carefully controlled in order to experimentally describe the absorption of vapors. In the case of vapors, surface area exposed may be the exposed parts of hands and face or effectively the whole body if loose, non-airtight clothing is worn. Piotrowski (1967) investigated the penetration of nitrobenzene vapors in clothed and naked volunteers at 10 mg/m^3 concentration in the air. The absorbed dose of nitrobenzene was reported as 13 mg in individuals wearing "normal working clothes" and 15 mg in individuals who were naked. Piotrowski (1971) also compared absorption of phenol vapors in clothed and naked volunteers and reported essentially the same total absorption in both cases. These studies suggest that the difference in absorption is much less than would be expected if the clothing were providing complete protection. The surface area of head and hands is 0.202 m^2, according to Table 8-3, approximately 10% of the total body surface area. If the clothing were providing complete protection, only 10% of the amount absorbed would be expected when compared to naked individuals. Until more information is available about the effect of clothing on vapor exposures, it is probably best to be conservative and assume that the whole body surface area is exposed, unless the clothing is impermeable to vapors and the openings around the neck, hands, and feet are closed.

Skin condition is another important parameter that should be taken into account in the risk assessment process. Obviously broken or damaged skin may be more permeable to vapors, but the temperature of the skin and the humidity of the air may also contribute. Piotrowski (1967) studied the effects of temperature and humidity on exposure to 10 mg/m^3 of nitrobenzene vapor. Naked individuals exposed at a temperature of 25°C absorbed 15 mg at 35% relative humidity and 23 mg at 67% relative humidity. Naked individuals exposed at a temperature of 25°C and 35% relative humidity absorbed 14 mg, while others exposed at a temperature of 30°C and 25% relative humidity absorbed 13 mg. These results suggest that humidity has a greater effect on penetration of chemical vapors than temperature, and the effect may be due to hydration of the skin either by sweating or decreasing evaporative water loss.

Loss of a chemical from diffusion out of the skin after a vapor exposure ends or when a volatile chemical is absorbed by another route, may or may not be a significant process to consider. Peck and coworkers (1981) have shown that chemicals migrate from the blood supply through the skin. The same diffusion processes should occur for volatile chemicals out of the skin as for absorption. However, the driving force (difference in concentration between the blood and air) may be much less than the driving force during a vapor exposure (difference in concentration between the air and blood).

7.2. EXPERIMENTALLY DERIVED VALUES

There is quantitative information available on the penetration rates of several chemical vapors and gases in humans and laboratory species. This information is based on determination of the total amount of chemical absorbed, flux, or permeability constants. Both in vivo and in vitro techniques have been used to obtain dermal absorption rate measurements for chemical vapors. These experimentally derived values will be discussed according to general categories into which the studies fall.

7.2.1. Human In Vivo

Several studies involving limited numbers of human volunteers have been reported in the literature. These studies are summarized in Table 7-1. Phenol vapor absorption at concentrations between 5 and 25 mg/m^3 was studied in individuals who were provided fresh breathing air from outside the chamber and were wearing underwear and denim overalls (Piotrowski, 1971). The exposure lasted for 6 hours with one break (of unspecified duration) in the middle and phenol absorption was estimated from colorimetric determination of phenol levels in the urine. Piotrowski (1967) also studied nitrobenzene absorption in volunteers wearing "normal working clothes" and estimated the absorption based on *p*-nitrophenol levels in the urine. Styrene vapor absorption has been studied in three volunteers who were clothed only in shorts and were wearing respirators connected to fresh breathing air (Wieczorek, 1985). Urine collection began half-way through the 2-hour exposure and continued until 24 hours after the exposure ended. The amount of styrene absorbed was determined by comparing the amount of urinary metabolites excreted during vapor contact to amounts of urinary metabolites excreted via inhalation studies. Riihimaki and Pfaffli (1978) exposed two volunteers wearing thin pajamas and socks, to 600 parts per million of styrene vapor while they cycled intermittently on a bicycle ergometer. Exhaled air samples and blood samples were used to back extrapolate the total amount of chemical absorbed based on known absorption from inhalation studies. Riihimaki and Pfaffli (1978) also exposed two volunteers to toluene, xylene, perchloroethylene, benzene, and methyl chloroform using the same experimental

Table 7-1. Estimated Human Permeability Constants for Vapor Phase Organic Chemicals[a]

Compound	C (mg/cm^3)	t (hr)	ABS (mg)	Flux (mg/cm/hr)	Vapor K_p (cm/hr)
Phenol[b]	5.05×10^{-6}	6.0	8.6		14.9
Phenol[b]	9.5×10^{-6}	6.0	13.8		12.7
Phenol[b]	2.4×10^{-5}	6.0	46.2		16.7
Nitrobenzene[c]	5.0×10^{-6}	6.0	7		12.3
Nitrobenzene[c]	1.0×10^{-5}	6.0	13		11.4
Styrene[d]	2.55×10^{-3}	3.5	60.1		0.35
Styrene[e]	3.25×10^{-3}	2.0	175.0		1.42
Styrene[e]	1.37×10^{-3}	2.0	45.0		0.87
m-Xylene[d]	1.30×10^{-3}	3.5	20.8		0.24
m-Xylene[d]	2.61×10^{-3}	3.5	44.5		0.26
Toluene[d]	2.26×10^{-3}	3.5	26.4		0.18
Perchloroethylene[d]	4.07×10^{-3}	3.5	47.1		0.17
Benzene[f]	1.00×10^{-3}	7.0	10.0		0.08
Aniline[g]	5.00×10^{-3}	6.0		1.90×10^{-4}	0.04
Aniline[g]	1.00×10^{-2}	6.0		2.50×10^{-4}	0.03
Aniline[g]	2.00×10^{-2}	6.0		4.00×10^{-4}	0.02
Methyl chloroform[d]	3.27×10^{-3}	3.5	2.1		0.01

[a] See text for equation; Vapor K_p estimated assuming skin surface area of 19,000 cm^2.
[b] Piotrowski, 1971.
[c] Piotrowski, 1967.
[d] Riihimaki and Pfaffli, 1978.
[e] Wieczorek, 1985.
[f] Hanke et al., 1961.
[g] Dutkiewicz and Piotrowski, 1961.

methods. Hanke et al. (1961) exposed two naked volunteers to benzene vapor and determined total absorbed based on urinary metabolites. Absorption of aniline vapor through the skin was investigated using an unspecified number of volunteers by Dutkiewicz and Piotrowski (1961). The absorbed dose or flux from these studies was used to calculate the permeability constants in Table 7-1 using the following relationship derived from Fick's first law (McDougal et al., 1990):

$$K_p^{air} = \frac{DA_{event}}{C_{air}\, t_{event}} \qquad (7.1)$$

where:

DA_{event} = The absorbed dose per event (mg/cm^2 - event)
A = Surface area exposed (cm^2)
C_{air} = Exposure concentration in air (mg/cm^3)
t_{event} = Exposure time (hr/event)

This calculation method assumes that absorption was constant during the exposure time and, therefore, may slightly underestimate the permeability constant at steady-state. The magnitude of the underestimate is directly related to the lag time and inversely related to the exposure time. The ranges of these permeability constants are over two orders of magnitude, with a high of 16.7 cm/hour for phenol and a low of 0.01 cm/hour for methyl chloroform. The permeability constants for phenol and nitrobenzene as determined by Piotrowski (1967, 1971), have considerably higher values than those determined by other investigators for fairly similar chemicals. These results suggest there may be some methodological or other reasons for these differences. These human studies were accomplished on very small sample sizes, were collected using various clothing and states of activity, and relied on determination of urinary metabolites and comparison with inhalation exposures; however, they are probably the best information available on human exposures to organic chemical vapors.

Hursh et al. (1989) recently conducted a study to investigate the dermal uptake of mercury vapor, a toxicologically significant inorganic compound. By measuring the difference between the accumulated radioactivity on exposed and unexposed forearms of human volunteers, these researchers were able to quantify the dermal uptake of mercury. The mean uptake rate for five subjects exposed to various mercury vapor concentrations was 0.024 ng mercury per cm^2 skin per minute per ng mercury per cm^3 air (units expressed by the authors). This value, however, probably represents both uptake into the systemic circulation and uptake and retention by the stratum corneum. The rate of uptake by skin was estimated as 2.6% of the rate of uptake by the respiratory tract. Desquamation of the stratum corneum causes loss of about half of the skin uptake (which is released by the outward movement of mercury-containing cells below the stratum corneum).

7.2.2. Human In Vitro

An alternative approach to estimating the permeability of chemical vapors through the skin was used by Scheuplein and Blank (1971). From measured solubilities of the compounds in the skin, data on the "sorption" of these compounds to dry stratum corneum tissue, and an assumed thickness of the stratum corneum, these investigators estimated gas-phase K_p^{air} values for a series of homologous alcohols and alkanes. These values are summarized in Table 7-2.

These studies were done with dry stratum corneum and diffusion constants were calculated from initial sorption rates when exposed to the vapor. The authors suggest that because the tissue was dry, the permeability constants were lower than would be expected with normally hydrated skin.

In addition to organic vapors, gases are also known to permeate the skin. Scheuplein and Blank (1971) summarized the results of investigators who obtained K_p^{air} values for permeant gases from studies of outward migration across the skin (Table 7-3).

These studies are the best information available, but the values presented in Table 7-3 have not been validated by recent investigators. There is no reason to believe that the permeability constant for intact skin would be different whether the penetration is "outside to in" or "inside to out."

Table 7-2. Estimated Permeability Coefficient Values (cm/hour) for Alcohol and Alkane (Saturated Vapors)

Compound Carbon Number	Alcohols	Alkanes
C_1	0.05	
C_2	0.02	
C_3	0.01	
C_4	0.02	0.0016
C_5	0.04	0.0062
C_6	0.12	0.0104
C_7	0.11	0.022
C_8	0.04	0.058
C_9	0.05	0.103
C_{10}	0.05	0.124
C_{11}		0.254
C_{14}		0.92

Source: Scheuplein and Blank (1971)

Table 7-3. Flux and Permeability Coefficient Values for Permeant Gases in Humans

Chemical	Flux (μmole/cm^2/hour)	K_p (cm/hour)
Helium	0.18	0.67
Argon	0.20	0.21
Nitrogen	0.11	0.25
Carbon Dioxide	0.49	0.24
Oxygen	0.49	0.46
Water	27.8	0.0007

Source: Scheuplein and Blank (1971)

Barry et al. (1985) obtained flux values for a number of organic compounds permeating human skin in vitro as either a vapor or a neat liquid (Table 7-4). These investigators used the upper 0.4 mm of whole skin clamped between a closed donor reservoir, which contained liquid to generate a saturated vapor, and a stirred receptor solution, which was 50% v/v aqueous ethanol. Vapor and liquid penetration were compared, and the integrity of the skin was assessed using tritiated water according to the following schedule: day 1 - tritiated water, day 2 - vapor diffusion, day 3 - liquid diffusion, and day 4 - tritiated water. Only fluxes were reported since the concentration of saturated vapor in the vapor studies was not determined. Fluxes from the liquid studies were quite a bit higher; however, if permeability constants could be calculated, the vapor permeability constants would probably be higher than the permeability constants from liquid because of the much greater concentration in the liquid form.

Table 7-4. Flux Values for Organic Compounds Permeating Human Skin In Vitro as a Saturated Vapor and as a Liquid

Compound	Flux[a] (μg/cm²/hour)	
	Vapor	Liquid
Anisole	420 ± 100	990 ± 300
Benzaldehyde	410 ± 70	1,970 ± 720
Aniline	260 ± 50	1,870 ± 1,260
Benzyl alcohol	52 ± 12	540 ± 240
2-Phenylethanol	27 ± 8	650 ± 60

[a] Flux (± sd)

Source: Barry et al. (1985)

These studies were accomplished with human skin that was frozen and then dermatomed to 0.4 mm. Due to the repeated exposures to the same chemical of the same skin sample, it is possible that the vapor penetration studies (day 2) could have affected the liquid studies (day 3) since they stated that it took up to 48 hours for full desorption. Since some of the chemical from the vapor studies could have remained in the skin at the time of the liquid studies, there is a possibility that any amount remaining would shorten the lag time and possibly impact the overall flux at early time points. These are the only studies available that were conducted to determine vapor absorption for these chemicals.

7.2.3. Primates In Vivo

Only one study (Hefner et al., 1975) is available that was conducted to determine the permeability of vapors in rhesus monkeys. These authors exposed anesthetized monkeys that were on a ventilator (to protect from inhalation exposure) to 7,000 and 800 ppm [^{14}C]vinyl chloride for 2 or 2.5 hours in a static chamber. Exhaled air and tissue concentrations were determined immediately after the exposure. They reported 0.787 mg and 0.121 mg total absorbed for the 7,000 ppm and 800 ppm exposures, respectively. If it is assumed that the surface area exposed for the monkeys was 3,450 cm^2, permeability constants can be calculated to be 6.4×10^{-6} cm/hour and 6.9×10^{-6} cm/hour, respectively. This study suggests that vinyl chloride vapor is not very permeable (see also Table 7-7).

7.2.4. Rodents In Vivo

In vivo exposures have been conducted by placing rats (McDougal et al., 1986, 1990; Clewell et al., 1988) or anesthetized mice (Tsuruta, 1989) in whole-body exposure chambers while providing respiratory protection. In the rat studies, concentrations of chemicals in blood were measured over a 4-hour exposure period. A physiologically based pharmacokinetic (PBPK) model was used to select the K_p^{air} values that gave a best least-squares fit to the blood concentration-time profile data. Tsuruta and coworkers determined vapor permeability in anesthetized ventilated mice by determining whole body concentrations and assuming linear kinetics. These values are summarized in Table 7-5 and 7-6.

These in vivo pharmacokinetic studies in rodents provide data that have the best potential for estimating vapor permeability constants for risk assessments when human data are not available, because they can be extrapolated to humans using PBPK models. Rodents have different skin structures as a result of the fur, and the amount of chemical that can be absorbed through the tail has never been addressed, so some caution is required in extrapolation to humans. Most of the evidence suggests that rodent skin is more permeable than human skin, therefore, measurements in rodents are likely to overestimate exposures. These methods rely on indirect measurement of blood concentrations to determine total absorbed, but careful experimentation can provide a mass balance. Physiologically based pharmacokinetic models are especially useful for chemicals in which metabolism is nonlinear, since important metabolic pathways can be explicitly incorporated, and the distribution, elimination, and metabolism of chemicals can be addressed dynamically. See McDougal (1991) for review of PBPK modeling in the skin.

Table 7-5. Dermal Vapor Absorption in Rats In Vivo

Compound	Concentration (ppm)	Flux (mg/cm^2/hour)	Permeability Constant[a] (cm/nour)
Styrene	3,000	0.0211	1.753 ± 0.105
m-Xylene	5,000	0.0151	0.723 ± 0.003
Toluene	8,000	0.0206	0.721 ± 0.007
Perchloroethylene	12,500	0.0541	0.668 ± 0.080
Benzene	40,000	0.0191	0.152 ± 0.006
Halothane	50,000	0.0180	0.045 ± 0.005
Hexane	60,000	0.0065	0.031 ± 0.004
Isoflurane	50,000	0.0096	0.025 ± 0.004

[a] Permeabilities are expressed as means ± SD, which are obtained by an estimation program. These numbers are not a measure of the variability in the rat population, but reflect the confidence that could be placed on the mean value for permeability.

Source: McDougal et al. (1990)

Table 7-6. Vapor Permeability Constants in Rodents[a]

Compound	K_p (cm/hr)
Dibromomethane[b]	1.32
Toluene[c]	1.24
Perchloroethylene[c]	1.00
Bromochloroethane[b]	0.79
1,1-Dimethylhydrazine (UDMH)[d]	0.7
Benzene[c]	0.69
Methylene chloride[b]	0.28
Hydrazine[d]	0.09

[a] Vapor permeabilities are an average of permeabilities at 3 or 4 concentrations.
[b] McDougal et al. (1986).
[c] Tsuruta (1989).
[d] Clewell et al. (1988).

The relationship between lipid solubility and dermal permeability for a number of organic compounds in the vapor phase suggest that a linear regression equation using these variables may serve as a useful tool to provide order-of-magnitude predictions of the K_p^{air} for similar compounds. The following regression equation (Equation 7.2) was derived using the K_p^{air} and fat/air partition coefficient data provided by McDougal et al. (1990):

$$K_{p(est)}^{air} = (K_{f/a} \times 0.00049) - 0.385 \qquad (r^2 = 0.956) \tag{7.2}$$

where:

$K_{p(est)}^{air}$ = Expected (estimated) K_p value (cm/hour)
$K_{f/a}$ = Fat/air partition coefficient

Equation 7.2 can be used to estimate $K_{p(est)}^{air}$ values of organic vapors when the fat/air partition coefficients fall within the range of values for isoflurane (98.1 ± 4.6) and styrene (3,476 ± 73), which is the range of chemicals on which the regression was performed. Values outside of this range would require extrapolation and engender greater uncertainty. $K_{p(est)}^{air}$ values have been estimated from fat/air partition coefficients within the range of the 55 volatile chemicals (Table 7-7) for which Gargas et al. (1989) reported partition coefficient data in F344 rats at 37°C. Fat/air partition coefficients larger than those for styrene (JP-10, m-styrene, and p-styrene) were not used in the regression equation due to uncertainty in the extrapolation. Fat/air partition coefficients for eleven chemicals were less than those for isoflurane, and $K_{p(est)}^{air}$ values were not calculated.

7.3. EQUATIONS FOR ESTIMATING THE DERMAL ABSORPTION OF CHEMICAL VAPORS

When permeability constants, flux or total absorbed, is available for humans or other species, dermal absorption can be estimated for a particular scenario of interest. When human data is not available, judgement needs to be used to decide whether to use the laboratory animal information as is or attempt to scale it to humans. In most cases, penetration data for rodents will be greater than humans and will, therefore, provide a conservative estimate of the exposure. However, these values would not provide conservative estimates for use in dose-response assessment of health effects. Techniques for estimating compound-specific K_p^{air} values for chemical vapors in the absence of experimental data have not been reported.

7.3.1. When Permeability Constant Is Available

When a vapor permeability constant is available (i.e., either experimentally derived or estimated), the amount absorbed can be calculated for a particular time, surface area exposed and concentration according to:

$$DA_{event} = K_p^{air} \, C_{air} \, t_{event} \tag{7.3}$$

Table 7-7. Estimated K_p^{air} Values Calculated From Fat/Air Partition Coefficient Data[a,b,c].

Chemical	Fat/Air Partition Coefficient	$K_{p(est)}^{air}$ (cm/hour)
Methanes		
Methyl chloride	13.5 ± 0.4	< 0.01[d]
Dichloromethane	120 ± 6	0.020
Chloroform	203 ± 5	0.061
Carbon tetrachloride	359 ± 11	0.137
Difluoromethane	1.43 ± 0.31	< 0.01[d]
Fluorochloromethane	15.4 ± 1.0	< 0.01[d]
Bromomchloromethane	325 ± 3	0.121
Dibromomethane	792 ± 14	0.350
Chlorodibromomethane	1,917 ± 165	0.901
Ethanes		
Chloroethane	38.6 ± 0.7	< 0.01[d]
1,1-Dichloroethane	164 ± 4	0.042
1,2-Dichloroethane	344 ± 5	0.130
1,1,1-Trichloroethane	263 ± 12	0.090
1,1,2-Trichloroethane	1,438 ± 58	0.666
1,1,1,2-Trichloroethane	2,148 ± 82	1.01
1,1,2,2-Trichloroethane	3,767 ± 93	1.81
Pentachloroethane	4,118 ± 209	1.98
Hexachloroethane	3,321 ± 193	1.59
1,2-Dibromoethane	1,219 ± 50	0.559
1-Bromo-2-Chloroethane	959 ± 39	0.431
1,1,1-Trifluoro-2-chloroethane	21.2 ± 0.6	< 0.01[d]
1,1,1-Trifluoro-2-bromo-2-chloroethane	182 ± 5	0.051

Table 7-7. (continued)

Chemical	Fat/Air Partition Coefficient	$K_{p(est)}^{air}$ (cm/hour)
Propanes		
1-Chloropropane	118 ± 2	0.019
2-Chloropropane	68.4 ± 2.0	< 0.01[d]
1,2-Dichloropropane	499 ± 30	0.206
n-Propyl bromide	236 ± 6	0.077
Isopropyl bromide	158 ± 5	0.039
1-Nitropropane	506 ± 33	0.209
2-Nitropropane	155 ± 4	0.03
Aliphatics		
n-Hexane	159 ± 2	0.039
n-Heptane	379 ± 6	0.147
Cyclohexane	235 ± 4	0.077
2,3,4-Trimethylpentane	443 ± 20	0.179
2,2,4-Trimethylpentane	293 ± 10	0.105
JP-10 (tricyclo[5.2.1.$0^{2,6}$]-decane	10,139 ± 239	not estimated[e]
Ethylenes		
Vinyl chloride	20 ± 0.7	< 0.01[d]
1,1-Dichloroethylene	68.6 ± 2.1	< 0.01[d]
cis-1,2-Dichloroethylene	227 ± 11.073	0.073
trans-1,2-Dichloroethylene	148 ± 11.034	0.034
Trichloroethylene	554 ± 21	0.233
Tetrachloroethylene	1,638 ± 91	0.764
Vinyl bromide	49.2 ± 1.3	< 0.01[d]

Table 7-7. (continued)

Chemical	Fat/Air Partition Coefficient	$K^{air}_{p(est)}$ (cm/hour)
Aromatics		
Benzene	499 ± 12	0.206
Chlorobenzene	1,277 ± 43	0.587
Toluene	1,021 ± 11	0.462
Styrene	3,476 ± 73	1.665
m-Methylstyrene	11,951 ± 692	not estimated[e]
p-Methylstyrene	11,281 ± 972	not estimated[e]
o-xylene	1,877 ± 132	0.881
m-xylene	1,859 ± 93	0.872
p-xylene	1,748 ± 65	0.818
Other Compounds		
Diethyl ether	47.7 ± 3.9	< 0.01[d]
Isoflurane	98.1 ± 4.6	0.010
Allyl chloride	101 ± 2	0.011
Isoprene	72 ± 2.4	< 0.01[d]

[a] Regression based on McDougal et al. (1990).
[b] Fat/air partition coefficient data of Gargas et al. (1989).
[c] Fischer 344 rats at 37°C.
[d] Fat/air partition coefficient too low to interpolate.
[e] Fat/air partition coefficient too high to interpolate.

where:

DA_{event} = Dose absorbed (mg/cm^2-event)
K_p^{air} = Vapor permeability constant (cm/hour)
C_{air} = Concentration in air (mg/cm^3)
t_{event} = Exposure time (hours/event)

This equation describes the steady-state situation because the K_p^{air} is determined at steady-state or calculated from a steady-state flux. As discussed in Chapter 4, this equation will underestimate the amount absorbed due to lack of consideration of nonsteady-state conditions. As mentioned in the introduction to this chapter, these procedures have not yet been developed for vapor exposure.

Additionally, dose absorbed per day can be calculated according to:

$$DA_t = DA_{event} \ x \ A \ x \ EV \tag{7.4}$$

where:

DA_t = Total dose absorbed per day (mg/day)
DA_{event} = Dose absorbed per event (mg/cm^2-event)
A = Surface area exposed (cm^2)
EV = Total number of events in seven days divided by 7 (events per day)

The calculated dose absorbed can be compared with dose absorbed from another route of absorption like inhalation or, with health risk estimates, converted to mass units by the use of appropriate extrapolations. For example, an inhalation RfC expressed in mg/m^3/day can be adjusted by the assumed ventilation rate or ventilation pattern per day (m^3) to yield a health risk estimate for noncancer toxicity expressed in mg/day for comparison. See Section 7.4. for a discussion of risk characterization of toxicity due to dermal absorption.

7.3.2. When Permeability Constant Is Not Available but Flux or Total Absorbed Is Available

When the flux has been determined, and the exposure concentration is known and constant, the permeability constant can be estimated by:

$$K_p^{air} = \frac{J_{ss}}{C_{air}} \tag{7.5}$$

where:

J_{ss} = Flux (mg/cm^2/hr)
C_{air} = Concentration (mg/cm^3)

This equation (modified from Equation 4.1) assumes that the concentration on the interior of the skin is zero, and the external concentration (C_{air}) is the concentration difference across the skin. This equation will slightly overestimate K_p^{air}.

When neither the K_p^{air} nor the flux are reported, but there is an estimate of total absorbed, Equation 7.1 can be used to determine K_p^{air} from the total absorbed, provided surface area exposed, exposure concentration in the air, and exposure time are known. If flux is reported, it can be substituted in Equation 7.6 to estimate the K_p^{air} that is used to estimate the exposure in Equation 7.3 or 7-4.

7.3.3. When No Permeability Data Are Available

When no permeability data are available, the last resort would be to estimate K_p^{air} based on octanol/water partition coefficients. This would be a very uncertain procedure due to the lack of appropriate information on vapor permeabilities and therefore such procedures are not recommended for vapors.

7.4. DECISION TREE FOR RISK CHARACTERIZATION OF TOXICITY DUE TO DERMAL ABSORPTION OF CHEMICAL VAPORS

The equations presented in Section 7.3. can be used to characterize the risk of dermal toxicity or toxicity remote from the skin as the portal-of-entry. The equations provide estimates of exposures that can then be compared to risk estimates of health effects for risk characterization. The decision tree (Figure 7-1) is a schematic of this process. The steps in the process are delineated below.

7.4.1. Determination of Maximum Achievable Concentration

The first step in ascertaining whether or not a chemical may pose a hazard due to dermal uptake of a vapor is to determine whether or not the chemical has a vapor pressure that will allow a significant concentration in air to be achieved at the temperature and atmospheric pressure of the scenario under evaluation. Use of the following equation permits estimation of the maximum achievable concentration (Barrow, 1989) by converting partial pressure to ppm:

$$Max\ Achievable\ Conc\ (ppm) = \frac{P_a^{vap}\ (mmHg)}{760\ (mmHg)} \ x\ (10^6\ ppm) \tag{7.6}$$

where:

P_a^{vap} = Vapor pressure (mmHg) exerted when a liquid is in equilibrium with its own vapor at a given temperature (°Kelvin)

760 (mmHg) = Atmospheric pressure

Reference texts such as the Handbook of Chemistry and Physics or the Merck Index may contain the needed information on vapor pressure. Chapter 7 Appendix provides a discussion of the calculation of vapor pressure when this information is not readily available in reference texts.

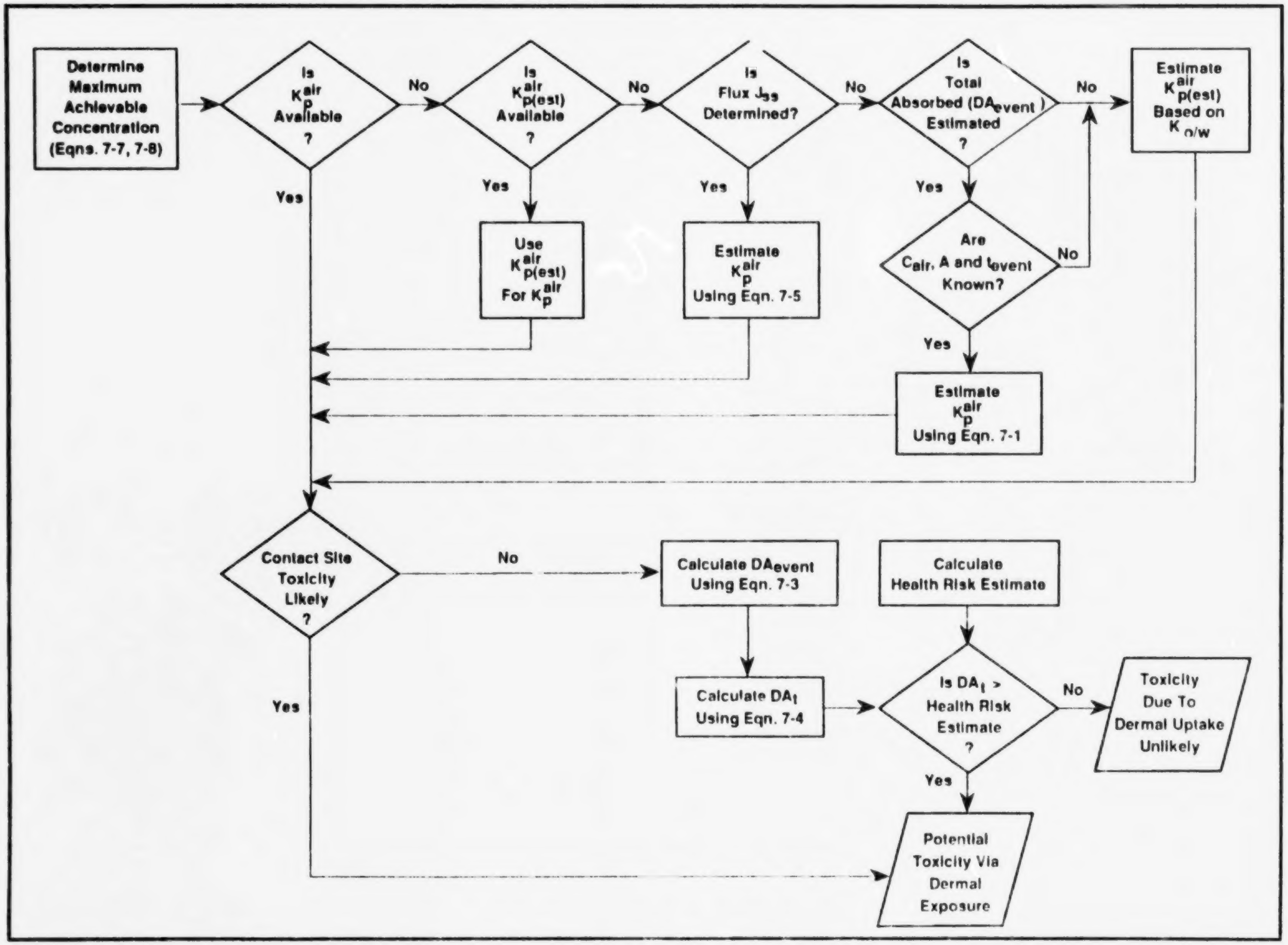
Determine Maximum Achievable Concentration (Eqns. 7-7, 7-8)
Is K_p^{air} Available ?
Yes
No
Is $K_{p(est)}^{air}$ Available ?
Yes
No
Use $K_{p(est)}^{air}$ For K_p^{air}
Is Flux J_{ss} Determined?
Yes
No
Estimate K_p^{air} Using Eqn. 7-5
Is Total Absorbed (DA_{event}) Estimated ?
Yes
No
Are C_{air}, A and t_{event} Known?
Yes
No
Estimate K_p^{air} Using Eqn. 7-1
Estimate $K_{p(est)}^{air}$ Based on $K_{o/w}$
Contact Site Toxicity Likely ?
No
Yes
Calculate DA_{event} Using Eqn. 7-3
Calculate DA_t Using Eqn. 7-4
Calculate Health Risk Estimate
Is DA_t > Health Risk Estimate ?
No
Yes
Toxicity Due To Dermal Uptake Unlikely
Potential Toxicity Via Dermal Exposure

Figure 7-1. Decision tree for risk characterization of toxicity due to dermal absorption.

For exposure levels expressed as ppm, the Ideal Gas Law can be used to derive the corresponding mass per volume (mg/m^3) level (EPA, 1990c):

$$mg/m^3 = ppm \times \frac{gmole}{22.4\ L} \times \frac{MW\ (g)}{gmole} \times \frac{273^oK}{T_a\ (^oK)} \times \frac{P_a\ (mmHg)}{760\ mmHg} \times \frac{10^3\ L}{m^3} \times \frac{10^3\ mg}{g} \quad (7.7)$$

where:

ppm = Concentration expressed on a volumetric basis 1 L/10^6 L

22.4 L = The volume occupied by 1 gmole of any compound in the gaseous state at 0°C and 760 mmHg

MW = Molecular weight in g/gmole

T_a = Actual temperature in degrees Kelvin

P_a = Actual pressure in mmHg

At 25°C and 760 mmHg, 1 gmole of perfect gas or vapor occupies 24.45 L. Therefore, under these conditions, the conversion of ppm to mg/m^3 becomes:

$$mg/m^3 = ppm \times \frac{MW\ (g)}{gmole} \times \frac{gmole}{24.45\ L} \times \frac{10^3 L}{m^3} \times \frac{10^3 mg}{g} \quad (7.8)$$

7.4.2. Determination of Permeability Constant

Vapor permeability constants are required to calculate the dose absorbed per day (DAD). Analogous to the discussion in Section 7.3., the decision tree outlines the order of preference for obtaining this parameter for use in the calculations of DA_t.

7.4.3. Potential for Contact Site Toxicity

The potential for portal-of-entry effects may be readily available from reference materials routinely used for hazardous material response and public right-to-know documentation. These references include the Merck Index, Patty's industrial Hygiene and Toxicology, Material Safety Data Sheets (supplied by the manufacturer for each chemical), the Occupational Health Guidelines published by the U.S. Department of Health and Human Services, the U.S. Department of Transportation's Emergency Response Guidebook, the Permissible Exposure Limits of the Occupational Safety and Health Administration (OSHA), and the Threshold Limit Values published by the American Conference of Governmental Industrial Hygienists (ACGIH). All of these documents provide information on the irritation and corrosivity potential of compounds.

Additionally, as mentioned in the introduction of this chapter, schemes have been developed to categorize gases as stable, reactive, metabolizable, or transition for the purpose of grouping by mode of uptake for the inhalation route of exposure (Dahl, 1990). Since gases that are reactive with respiratory tissue could also readily react with the skin, the reader is referred to this categorization scheme for further information on determining the potential reactivity of a gas.

If it is determined that the compound has the potential for contact site toxicity, the amount of chemical in the skin could be determined for the steady-state condition where the skin vehicle partition coefficient is known:

$$C_{skin} = K_{s/air} \times C_{air} \tag{7.9}$$

where:

$K_{s/air}$ = Skin/air partition coefficient
C_{air} = Concentration to which the skin is exposed

This concentration in the skin is the concentration that would be expected at equilibrium. In the human exposure situation, this is unlikely to occur in most situations because of the time required at a constant concentration to reach steady-state. Skin/air partition coefficients are also not readily available for a wide variety of chemicals.

7.4.4. Choice of Health Risk Estimates

The choice of a health risk estimate by which to gauge toxicity may be somewhat difficult since investigations are not routinely performed by this route. Skin painting studies are done to evaluate contact sensitivity and for carcinogenic potential, but the dosimetric definition of the dose to the skin for these types of studies is limited as described above. There are some citations of toxicity noted for dermal exposures, however, and these would be appropriate to consider as a basis for health risk estimates. The type of toxicity, i.e. cancer or noncancer, would determine the type of methodology to employ to calculate a health risk estimate (inhalation or oral unit risk values and inhalation reference concentrations or oral reference doses, respectively). Methodologies have been published on how to derive these health risk estimates and are beyond the scope of this chapter (Barnes and Dourson, 1989; EPA, 1987b, 1990c).

Another alternative to calculating health risk estimates is to use values established for other routes and convert these to the dermal route. Guidance on performing route-to-route extrapolations is provided elsewhere (EPA, 1990c; 1990e).

The concentration-response relationship for contact site toxicity is usually established empirically, although it may be possible to make crude comparisons if the metric for toxicity was based on surface area involved. For example, the inhalation RfC for respiratory effects is based on the amount of compound deposited per minute per cm^2 of respiratory surface area for the region in which the health effect was observed and expressed as a concentration, mg/m^3. This value could be converted by the default ventilation rate or ventilatory activity pattern (m^3) to obtain an estimate of the amount in mg likely to cause irritation. Since compounds that cause respiratory irritation are also likely to cause dermal irritation, this may provide a health risk estimate by which to characterize risk. Equations for non-steady state and for determination of the amount in skin tissue, as well as laboratory validation of these procedures, are required to adequately address direct dermal toxicity.

Generally, a route-to-route extrapolation for toxicity remote to the portal-of-entry should be based on some internal metric (e.g., area under the blood concentration curve) that bears an identifiable relationship to the target tissue toxicity. A crude estimate for screening purposes may be calculated from other routes by converting values for toxicity remote to the portal-of-entry via other routes by the assumed default parameters to back extrapolate the values to mg associated with remote toxicity.

7.4.5. Risk Characterization

Risk characterization involves the comparison of the exposure estimate with a given estimate for health risk and a discussion of the inherent uncertainty in the assumptions used to describe the scenario and the resultant characterization. For example, more uncertainty would be engendered in a risk characterization that was based on exposure estimates calculated from estimated K_p^{air} values compared to health risk estimates derived from route-to-route extrapolation using default parameters than there would be in a characterization that resulted from the comparison of exposure estimates based on measured K_p^{air} values to route-specific toxicity estimates. Concern of health risk increases as the exposure estimate exceeds that of the health risk, although this should be couched in terms of the precision of the health risk estimate. For example, the precision of the oral RfD or inhalation RfC is no greater than an order of magnitude.

7.5. RISK CHARACTERIZATION CASE STUDY OF N-HEXANE

This section provides an example risk characterization of toxicity due to dermal absorption of n-hexane according to the steps outlined in Section 7.4. The scenario of interest is to evaluate exposures at 20°C and atmospheric pressure. The exposures last 6 hours per day, 5 days per week.

7.5.1. Determination of Maximum Achievable Concentration

Since neither the Handbook of Chemistry and Physics nor the Merck Index provide a vapor pressure in addition to the boiling point, Equation 7.11 of Chapter 7 Appendix is used to calculate the vapor pressure for n-hexane. The temperature of interest is 20°C and the atmospheric pressure is at sea level.

$$\log P_a^{vap} = \frac{4.6}{T_a}(T_a - T_b)$$

$$\log P_a^{vap} = \frac{4.6}{293}(293-342) = -0.769 \qquad (7.10)$$

$$P_a^{vap} = 0.17\ atm$$

where:

P_a^{vap} = Vapor pressure at T_a (atm)
T_a = Temperature of interest (20°C), in degrees Kelvin (293°K)
T_b = Boiling point (69°C) at 1 atmosphere, in degrees Kelvin (342°K)

The vapor pressure in atmospheres is then converted to mmHg (1 atmosphere = 760 mmHg):

$$0.17\ atmospheres = 129.2\ mmHg \qquad (7.11)$$

The vapor pressure in mmHg is then used in Equation 7.7 to calculate the maximum achievable concentration in ppm:

$$\begin{matrix} MAX\ ACHIEVABLE \\ CONCENTRATION \end{matrix} = \frac{129.2\ mmHg}{760\ mmHg} \ x\ 10^6\ ppm = 170{,}000\ ppm \qquad (7.12)$$

And then Equation 7.7 is used to convert ppm to mg/m^3:

$$\begin{aligned} mg/m^3 &= ppm\ x\ \frac{gmole}{22.4\ L}\ x\ \frac{MW\ (g)}{gmole}\ x\ \frac{273^oK}{T_a}\ x\ \frac{P_a}{760mmHg}\ x\ \frac{10^3\ L}{m^3}\ x\ \frac{10^3\ mg}{g} \\ &= \frac{170{,}000\ parts}{10^6\ parts}\ x\ \frac{gmol}{22.4\ L}\ x\ \frac{86.18g}{gmole}\ x\ \frac{273^oK}{293^oK}\ x\ \frac{760\ mmHg}{760\ mmHg} \\ &\qquad x\ \frac{10^3\ L}{m^3}\ x\ \frac{10^3\ mg}{g} \\ &= 0.61\ x\ 10^6\ mg/m^3 \end{aligned} \qquad (7.13)$$

ppm = Concentration expressed on a volumetric basis 1 L/10^6 L

86.18 = Molecular weight (g/gmol)

22.4 L = The volume occupied by 1 gmol in the gaseous state at 0°C and 760 mmHg

T_a = Actual temperature in °Kelvin

P_a = Actual pressure in mmHg

7.5.2. Determination of Permeability Constant

Since there is an experimental K_p for n-hexane (Table 7-5), the value of 0.031 cm/hour is used for calculations of dose absorbed (DA_{event}).

7.5.3. Dose Estimation

The potential for both systemic toxicity and contact site toxicity for n-hexane is well documented. The Occupational Health Guideline (U.S. DHHS) notes that n-hexane "can affect the body if it is inhaled, comes in contact with the eyes or skin, or is swallowed." Skin disease is listed to occur as a result of long-term exposures due to its defatting nature. Polyneuropathy, narcosis, and respiratory tract irritation are also identified as potential disease outcomes.

Using Equation 7.3, the DA_{event} at steady-state flux is calculated:

$$\begin{aligned} DA_{event} &= K_p^{air} \ x \ C_{air} \ x \ t_{event} \\ DA_{event} &= 0.031 \ x \ 0.61 \ x \ 6 \\ &= 0.113 \ mg/cm^2\text{-}event \end{aligned} \qquad (7.14)$$

where:

DA_{event} = Dose absorbed at steady-state (mg/cm^2-event)

K_p^{air} = Vapor permeability constant (0.031 cm/hr)

C_{air} = Concentration in air (0.61 x 10^6 mg/m^3 = 0.61 mg/cm^3)

t_{event} = Exposure time (6 hrs/event)

The total dose absorbed per day (DA_t) for toxicity remote to the portal of entry is calculated from DA_{event} using Equation 7.4:

$$DA_t = DA_{event} \ x \ A \ x \ EV$$
$$DA_t = 0.113 \ x \ 19{,}000 \ x \ \frac{5}{7} = 1{,}540 \ mg/day \qquad (7.15)$$

where:

DA_t = Total dose absorbed per day (mg/day)
DA_{event} = Dose absorbed per event (0.113 mg/cm^2-event)
A = Surface area exposed (19,000 cm^2)
EV = Total number of events in 7 days divided by 7 (events per day)

7.5.4. Choice of Health Risk Estimate

The carcinogenic toxicity of n-hexane has not been evaluated. The noncancer toxicity of the compound has been well described and an inhalation reference concentration (RfC) has been calculated and is available on the Integrated Risk Information System (EPA, 1990b). The RfC is an estimate (with uncertainty spanning perhaps an order-of-magnitude) of a daily inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime (EPA, 1990c). There is no oral reference dose for n-hexane.

The inhalation RfC was based on both systemic toxicity (neurotoxicity) in occupationally exposed workers and on epithelial lesions in the nasal cavity of B6C3F1 mice. After dosimetric adjustments to extrapolate to human equivalent concentrations for continuous exposures, the RfC (mg/m^3) for both of these lesions resulted in the same estimate, 0.2 mg/m^3. This is chosen as the most appropriate health estimate by which to gauge the potential toxicity of n-hexane via dermal uptake. It should be noted that most often calculations for concentrations associated with respiratory toxicity and remote toxicity are not the same. Since the metric and likely the underlying mechanism of action for respiratory effects versus the remote toxicity are not the same, the choice of which estimate to use for back extrapolating a mg/day estimate should be based on these considerations.

7.5.5. Risk Characterization

The daily absorbed dose from dermal exposure calculated for steady-state (DA_t) can be compared with an amount back-extrapolated from the inhalation RfC value for n-hexane, since its basis is neurotoxicity remote to the portal of entry. Multiplication of the RfC (expressed as $mg/m^3/day$) by the default daily ventilation volume of 20 m^3 results in an amount (4 mg/day) with units comparable to the calculated exposure estimate. The uptake at steady-state, DA_t (1,540 mg/day), is above the inhalation RfC by 385-fold, indicating a potential for remote toxicity due to dermal exposure.

The literature indicates that the probability of toxicity remote to the portal-of-entry is greater than that of direct dermal toxicity, since skin toxicity occurred after prolonged exposures. As noted earlier, the degree of precision of the inhalation RfC is an order of magnitude, which suggests less concern over the potential systemic toxicity due to dermal uptake of n-hexane for this scenario is warranted due to its larger margin of exposure, and illustrates the potential for contribution to toxicity via this route. As mentioned earlier, further development of procedures for assessing non-steady state conditions and direct skin effects are needed to more fully address dermal toxicity.

CHAPTER 7 APPENDIX: CALCULATION OF VAPOR PRESSURE

If the vapor pressure at the temperature of interest is not readily available in reference texts, the following equation can be used to approximate the vapor pressure in atmospheres (O'Connor, 1977):

$$\log P_a^{vap} = \frac{4.6}{T_a}\left(T_a - T_b\right) \tag{7.16}$$

where:

P_a^{vap} = Vapor pressure of interest (atmospheres)
T_a = Temperature of interest (°Kelvin)
T_b = Boiling point temperature (°Kelvin) at 1 atm

Vapor pressure in atmospheres can then be converted to mmHg for use in Equation 7.7 by applying the conversion factor of 1 atmosphere/760 mmHg.

Equation 7.20 was derived from two empirical relationships. The first, known as Trouton's rule was determined from observation of various ways of graphing boiling point and heat of vaporization data for a series of compounds (Figure 7-2). An essentially linear plot results, corresponding to the general equation y = mx + b, when the normal boiling point (°Kelvin) is the y coordinate and the molar heat of vaporization (cal/mole) is the x coordinate. The slope of the line is approximately 21 (cal/mol°K) and the extrapolated y intercept is zero. As a result, Trouton's rule can be expressed as:

$$\Delta H_{vap} = 21\ T_b \tag{7.17}$$

Since "simple" liquids show the best correlation with the linear plot, Trouton's Rule is generally limited to approximations of ΔH_{air} from the measured boiling points of liquids of this type.

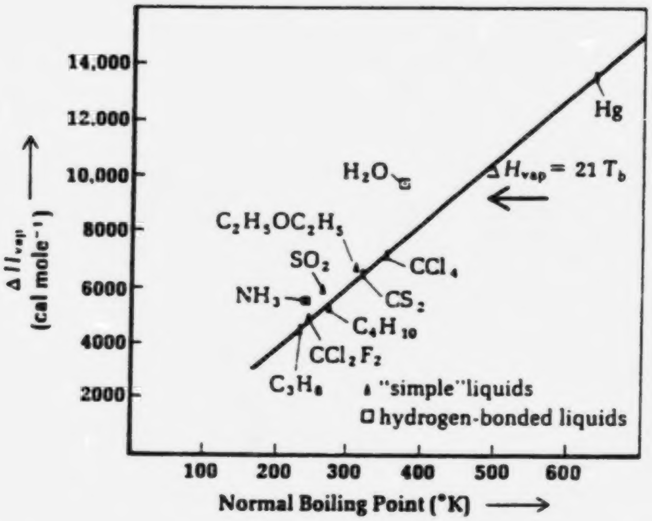

Figure 7-2. Empirical basis for Trouton's rule.
Source: O'Connor (1977)

The other relationship from which Equation 7.10 derives may also be determined from graphical displays of experimental data and reveals that a linear plot is obtained for a particular liquid if the y coordinate is the logarithm of absolute temperature (°Kelvin), i.e., 1/T. It should be noted that analysis of such graphical displays are typically the way vapor pressure is determined empirically for temperatures of interest when laboratory facilities are available to determine the data.

The particularly interesting feature of such plots, (Figure 7-3) is that the slope of the line for any specific liquid-vapor system is always found to be, within reasonable limits, a function of the molar heat of vaporization of the liquid:

$$\mathit{slope} = -\frac{\Delta H_{vap}}{4.6} \tag{7.18}$$

For any one of the linear relationships graphed in Figure 7-3, the equation for one line may be expressed as:

$$\log P^{vap} = -\left[\frac{\Delta H_{vap}}{4.6}\right]\left[\frac{1}{T}\right] + b \tag{7.19}$$

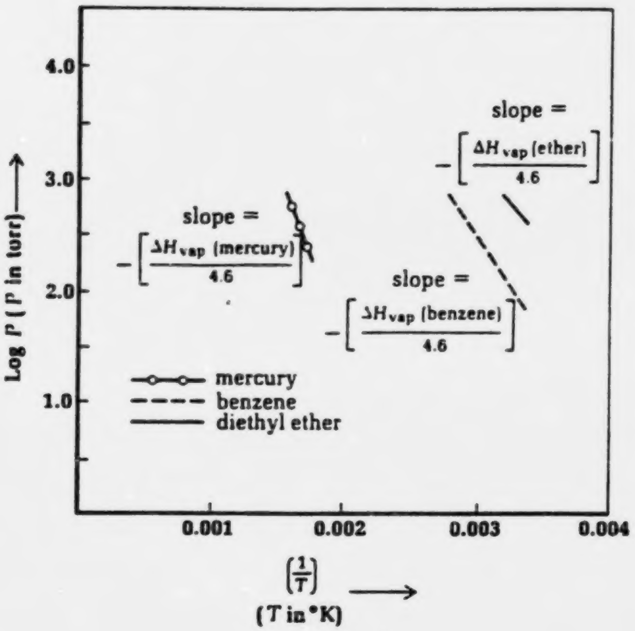

Figure 7-3. Variation of vapor pressure with temperature.

Source: O'Connor (1977)

It is rarely feasible to determine the y intercept (b), since the linearity of the plot is actually limited to a fairly narrow temperature range. However, if two sets of temperature, pressure coordinates are selected, it may be written:

$$\begin{aligned} \log P_a^{vap} &= -\left[\frac{\Delta H_{vap}}{4.6}\right]\left[\frac{1}{T_a}\right] + b \\ \log P_b^{vap} &= -\left[\frac{\Delta H_{vap}}{4.6}\right]\left[\frac{1}{T_b}\right] + b \end{aligned} \tag{7.20}$$

Then, by subtracting equalities:

$$\log\left(P_a^{vap} - P_b^{vap}\right) = \left[-\left[\frac{\Delta H_{vap}}{4.6}\right]\left[\frac{1}{T_a}\right] + b\right] - \left[-\left[\frac{\Delta H_{vap}}{4.6}\right]\left[\frac{1}{T_b}\right] + b\right] \tag{7.21}$$

from which:

$$\log\left[\frac{P_a^{vap}}{P_b^{vap}}\right] = \left[\frac{\Delta H_{vap}}{4.6}\right]\left[\frac{1}{T_b} - \frac{1}{T_a}\right] \tag{7.22}$$

or:

$$\log\left[\frac{P_a^{vap}}{P_b^{vap}}\right] = \left[\frac{\Delta H_{vap}}{4.6}\right]\left[\frac{T_a - T_b}{T_a T_b}\right] \tag{7.23}$$

This form of the equation is referred to as the Clausius-Clapeyron relationship. If we consider the mathematical formulation under the special condition in which T_b is the normal boiling point, so that P_b^{vap} is 1.0 atm, and use Trouton's Rule to approximate ΔH_{air}, then for "simple" liquids,

$$\log \left[\frac{P_a^{vap}}{1.0}\right] = \left[\frac{21\,T_b}{4.6}\right]\left[\frac{T_a - T_b}{T_a T_b}\right] \tag{7.24}$$

from which, with P_a^{vap} in atmospheres, Equation 7.10 is derived:

$$\log P_a^{vap} = \frac{4.6}{T_a}\left(T_a - T_b\right) \tag{7.25}$$

PART 2. APPLICATIONS OF DERMAL EXPOSURE ASSESSMENT

8. CHARACTERIZING DERMAL EXPOSURE SCENARIOS

This chapter presents procedures for characterizing dermal exposure scenarios. This involves estimating the number of people exposed, size of the exposed skin area, contact time, and amount or concentration of contaminant contacting the skin. Additionally a brief discussion is included on techniques for direct measurement of dermal contact. The principal focus of this chapter is limited to scenarios involving water and soil contact.

Many of the issues related to characterizing dermal exposure scenarios have been addressed in a number of existing EPA guidance documents, including:

- Methods for Assessing Exposure to Chemical Substances (EPA, 1983);
- Estimating Exposures to 2,3,7,8-TCDD (EPA, 1988a);
- Methodology for Assessing Health Risks Associated with Indirect Exposure to Combustor Emissions (EPA, 1990d);
- Superfund Exposure Assessment Manual (EPA, 1988b);
- Risk Assessment Guidance for Superfund (EPA, 1989b);
- Exposure Factors Handbook (EPA, 1989a); and
- Pesticide Assessment Guidelines, Subdivisions K and U (EPA, 1984a, 1986).

These documents serve as valuable information resources to assist in the assessment of dermal exposure. Much of the material presented in this chapter is derived from these documents, and the reader is encouraged to refer to them for a more detailed discussion.

Dermal exposure to environmental contaminants can occur during a variety of activities and may be associated with a number of different environmental media:

- Water (e.g., bathing, washing, swimming);
- Soil (e.g., outdoor recreation, gardening, construction);
- Sediment (e.g., wading, fishing);
- Liquids (e.g., use of commercial products);
- Vapors (e.g., use of commercial products); and
- Indoor dust (e.g., children playing on carpeted floors).

This document, and this chapter in particular, focusses primarily on water and soil exposure. However, contact with other media may also be important to consider, and it is hoped that they can be addressed in follow-up efforts. The following sections provide a background for understanding the dermal exposure variables used in the dermal exposure equations for soil and water. The range of possible values for each parameter is discussed along with recommended default values to be used when site-specific data are not available. The strategy for selecting default values is to express them as a range from a central value to a high end value of their distribution. Where statistical distributions are known, the central value corresponds to the mean and the high end value corresponds to the 90 or 95th percentile. Where statistical data are not available, judgement is used to select central and high end values. This strategy corresponds to the default selection strategy used in the Exposure Factors Handbook (EPA, 1989a). Note that the range of values is intended to represent variations that occur across a population. Ideally, assessors should also consider uncertainty in the actual value due to measurement error or other factors. The combination of these factors to derive an exposure estimate can create scenarios of varying severity. Ideally, these combinations would be made via statistical techniques such as Monte Carlo Analysis. However, this requires detailed knowledge of the distributions of each input variable, which is rarely available. Lacking such data, some general guidance can be offered as follows: use of all central values for each parameter should produce a central value scenario; use of all high end values for each parameter, produces a bounding estimate that is usually above the high end of the distribution; and a mix of high end and central values is probably the best way to create a reasonable high end scenario.

8.1. EXPOSED POPULATIONS

The initial steps of an exposure assessment involve determination of the pathways by which people are exposed to contaminants and identification and quantification of exposed populations. Detailed guidance for performing a quantitative population analysis is provided in the Superfund Exposure Assessment Manual (SEAM) (EPA, 1988b).

Populations that experience dermal exposure to ground-water or surface-water contaminants can be identified by recognizing geographically defined sources of recreational surface waters such as contaminated rivers, lakes, and ponds. Dermal contact with these waters results primarily from swimming. Quantification of the population exposed in this manner may be possible by contacting local governmental agencies concerned with recreation. In the absence of site-specific data, SEAM (EPA, 1988b) recommends using a national average value of 34% of the total population of the area to quantify the number of persons who swim outdoors in natural water bodies.

Populations potentially exposed to contaminated ground water or surface water also include persons served by a water supply system that draws its water supply from a contaminated source. Such a population may be dermally exposed while swimming in pools or bathing and washing. Information regarding local surface water or ground water sources, the populations served, and the number of households that draw water from private wells should be available from local public works or health departments.

Populations exposed by dermal contact with contaminated soil may include neighborhood children playing at contaminated sites, workers, and gardeners. The number of children and other age groups who live in areas where the soil is contaminated and are potentially exposed can be estimated by referring to census data.

8.2. CONTAMINATION OF ENVIRONMENTAL MEDIA

Since contaminants may be transported in environmental media as vapors, particulates, or in dissolved form, any contact with a medium that contains such substances can potentially result in dermal absorption. The extent of the dermal exposure and absorption of a specific contaminant from soil, water, sediments, or vapor can only be evaluated following a determination of the concentration of the contaminant in the medium of interest. The contaminant concentrations used in an exposure assessment should be representative of the location and time period where contact occurs. Exposure concentrations may be estimated using monitoring data alone, or as in most exposure assessments, using a combination of monitoring data and environmental fate and transport models. The selection and use of such models are explained in the following documents:

- Superfund Exposure Assessment Manual (SEAM) (EPA, 1988b);
- Exposure Factors Handbook (EPA, 1989a);
- Selection Criteria for Models Used in Exposure Assessments: Ground water Models (EPA, 1988c); and
- Selection Criteria for Mathematical Models Used in Exposure Assessments: Surface Water Models (EPA, 1987a).

8.3. EXPOSURE TIME, FREQUENCY, AND DURATION

Exposure time, frequency, and duration are three of the variables necessary for application of the dermal dose equations given in Chapter 10. Exposure or event time (i.e., hour/event) is the time over which a single contact event occurs. Event frequency (i.e., event/day or events/year) refers to how often the contact event occurs. The exposure duration time (expressed in units of years) can be defined as the overall time period over which dermal contact events occur. The following discussion summarizes the values for these parameters for dermal exposure to contaminants in soil and water.

8.3.1. Soil Contact Time, Frequency, and Duration

Activities associated with incidental soil ingestion are likely to present opportunities for dermal exposure. Hawley (1985) used existing literature and professional judgement to develop scenarios for estimating exposure of young children, older children, and adults to contaminated soil. These exposure time values are presented in Table 8-1. Hawley's assumptions included consideration of seasonal factors; estimates were divided into winter months, when soil contact would be limited in some parts of the United States, and summer months, when more opportunity existed for such contact. Hawley (1985) assumed an outdoor soil exposure of 5 days/week during a period of 6 months, for young children (2.5 years of age). The contact time was estimated to be approximately 12 hours, since children retain soil on their skin after coming indoors. For older children, the average outdoor playtime, during which dermal exposure to soil would occur, was estimated at 5 hours/day 6 days/week from May to September. Adults were estimated to be exposed to outdoor soil 8 hours/day 2 days/week during the warmer months.

Table 8-1. Assumptions of Outdoor Soil Exposure Time

Exposure Frequency & Duration	Age Class
12 hours/day, 5 days/week, 6 months/year	2.5 years
5 hours/day, 6 days/week, 5 months/year	older children
8 hours/day, 2 days/week, 5 months/year	adults

Source: Hawley, 1985

If the contaminated soil is carried into the house from the surrounding area, household dust may be contaminated at levels approaching those found outdoors (EPA, 1988a). Furthermore, indoor use of some commercial products, such as pesticides, may result in increased indoor contaminant levels. The frequency and duration of dermal contact with contaminated indoor dust may also need to be considered.

No actual data could be found on the residence times of soil residues on skin. It probably corresponds roughly to the time between washings or about 8 to 24 hours. Soil contact time (as discussed in Chapter 6) may influence the percent absorption value. It may also be useful for evaluating the experimental conditions used to generate percent absorption estimates. Since the residence times of soil residues on skin are probably in the range of 8 to 24 hours, experiments conducted over similar times would provide the best basis for percent absorption estimates.

A range of values for the frequency of soil contact has been developed in past exposure assessments. These frequencies were derived from considerations of seasonal factors that may influence activities and soil conditions. These are summarized in Table 8-2.

Table 8-2. Assumptions of Frequency of Exposure to Soil

Range	Reference
350 days/year	EPA, 1989b
247-365 days/year	EPA, 1984b
180 days/year	Paustenbach et al., 1986
130 days/year (<2-5 yr)	Hawley, 1985
130 days/year (older children)	Hawley, 1985
43 days/year (adults)	Hawley, 1985

The upper end of the range presented in Table 8-2 is based on the rationale that in warmer climates, people who actively garden or play outdoors could have contact with soil almost every day. However, in cooler climates, outdoor activities involving soil contact may occur only during about half of the year. Where the contaminated soil is located outside the residential property, contact may only occur a few days/year. In summary, this is a very site-specific value that could range from a few days/year to every day. For default purposes, a typical value for an adult who gardens or works outside 1 to 2 days/week during the warmer months may correspond roughly to Hawley's estimate (after rounding) of 40 days/year. For consistency with the default value for the frequency of soil ingestion recommended by EPA (1989b), an upper estimate of 350 days/year was selected.

The exposure duration over which soil contact could occur depends primarily on how long a person lives near a contaminated site. This factor is also a very site-specific value that could range from one year or less to a lifetime. EPA (1989a, 1989b) has reviewed census data and concluded that the time people spend at a residence averages about 9 years, with an upper estimate of 30 years. On this basis, a range of 9 to 30 years is recommended for default purposes.

8.3.2. Water Contact Time, Frequency, and Duration

Approximately 90% of the American population bathes every day, and 5% average more than one bath/day (Tarshis, 1981). Seventy-five percent of the men and 50% of the women use showers as a primary means of bathing. Since the range of likely values is so narrow, a single default value of 1 event/day, 350 days/year is recommended for bathing frequency.

The upper default of 350 days/year was selected over 365 days/year to reflect the probability that most people spend some time away from their residence, using water from a different source.

While no data have been presented to show gender or age differences in shower time, EPA (1989a) presented a cumulative frequency distribution of shower times for a population as a whole. Based on records of 2500 Australian households, shower times ranged from 2 to 20 minutes with a median of 7 minutes and a 90th percentile of 12 minutes (James and Knuiman, 1987). Furthermore, EPA (1989a) estimates that shower-flow rates range from 5 to 15 gallons/minute. Brown and Hattis (1989) assumed a 20-minute bath time to estimate the dermal absorption from hypothetical bathtub scenarios. Adding a few minutes for water residues to dry, a default range of 10 to 15 minutes is recommended.

Much less information is available on the time and frequency of swimming. The SEAM (EPA, 1988b) suggests that national average values based on the Department of the Interior (DOI) Bureau of Outdoor Recreation survey (DOI, 1973) be applied. These are:

Exposure Frequency:	7 days/year
Exposure Time:	2.6 hours/day

Further investigation of this survey revealed that the exposure time value represented more than actual time in water. The reliability of the frequency estimate also appears questionable. Accordingly, no reliable data on swimming time and frequency could be found and it is recommended that assessors make judgements of their own on a site-specific basis. Consideration should be given to geographic factors such as proximity or availability of surface waters for recreation and seasonal factors. Furthermore, certain subpopulations (e.g., competitive swimmers) will encounter a greater mean exposure frequency and time. Based on judgement, a reasonable average value for a recreational swimmer may be 5 days/year for 0.5 hours/event, 1 event/day and a reasonable upper value for a person who swims regularly for exercise or competition may be 150 days/year for 1 hour/event, 1 event/day.

The exposure duration for both swimming and bathing will be determined primarily by how long a person lives in one residence. As stated above, census data suggests that this averages about 9 years and has an upper estimate of 30 years. This range of 9 to 30 years is recommended for default purposes.

8.4. SKIN SURFACE AREA

This section describes how to obtain values for total body surface area and the surface area of component body parts that may be exposed to contaminated media. In addition, a discussion is included concerning the effect of clothing on determining the effective surface area exposed.

The U.S. EPA Exposure Factors Handbook (EPA, 1989a) and the Development of Statistical Distributions or Ranges of Standard Factors Used in Exposure Assessments (EPA, 1985) present reviews of measurement techniques that have been used in the past to estimate surface area. In addition, these documents present summary data for skin surface areas for different genders and ages.

Determination of the surface areas of the component body parts has been performed by a number of authors as part of their determination of whole body surface areas. The surface areas of anatomical parts have been reported by gender, age, and ethnic group. Early studies have reported surface areas for such component parts as head, trunk, upper arms, forearms, hands, thighs, legs, and feet. Unfortunately, these early studies were based on very limited numbers of subjects, and the values reported may not be meaningful when attempting to extrapolate to other populations. For example, Boyd's (1935) data set consists of measurements on two children measured at various intervals over less than a year. DuBois and DuBois' (1916) data set is limited to four adult males and one adult female. More extensive studies, such as those performed by Fujimoto and Watanabe (1969) are useful because of the number of subjects measured (201), but their applicability may be limited due to initial biases; this study is limited to Japanese subjects prescreened to fit a "standard Japanese physique."

EPA (1985) used available direct measurement data, including the Japanese data outlined above, to generate equations that estimated surface area of body parts as a function of height and weight. These equations were then applied to the U.S. adult population, using height and weight distribution data obtained from the National Health and Nutrition Examination Survey II (NHANES II) (NCHS, 1983). Insufficient data precluded the development of similar equations for children.

For adults, EPA (1985) used regression equations that relate height and weight to the surface area of the head, trunk, upper extremities, and lower extremities. Because of the low regression coefficient (r^2) values of the equations for male and female heads, and for female hands, the equations are considered to be inaccurate predictors of the surface area for these body parts.

EPA (1985) also estimated percentiles for the surface areas of body parts using the regression equations, and the NHANES II height and weight database. For children, the available measurements of the body part surface areas were summarized as a percentage of the total surface area. Data on the surface areas of specific body parts for adults and children are presented in the Exposure Factors Handbook (EPA, 1989a). Note that the percent of total body surface area contributed by the head decreases from childhood to adult status, whereas that contributed by the legs increases.

One inherent assumption of many exposure scenarios developed in the past is that clothing prevents dermal contact and, subsequently, absorption of contaminants. This assumption may in fact be faulty in cases where the contaminant is carried in a fine dust or liquid suspension, which may be able to penetrate clothing. Studies using personal patch monitors placed beneath clothing of pesticide workers show that a significant proportion of the dermal exposure may occur at anatomical sites covered by clothing (Maddy et al., 1983). Fenske (1988) has demonstrated that a "pumping" effect can occur which causes material to move under clothing. Furthermore, studies have demonstrated that hands cannot be considered to be protected from exposure even if waterproof gloves are worn. This may be because of contamination on the interior surface of the gloves, removal of gloves during machine adjustments, and handling of the outside of the gloves while putting them on or taking them off (Maddy et al., 1983). Depending on their specific tasks, pesticide workers have been shown to experience 12% to 43% of their total exposure through their hands, approximately 20% to 23% through their heads and necks, and 36% to 64% through their torsos and arms, despite the use of protective gloves and clothing (Fenske et al., 1985, 1986). These studies were conducted with fine mists and vapors. Clothing is expected to limit the extent of the exposed surface area in cases of soil contact. EPA (1989a) presents two adult clothing scenarios for outdoor activities:

Typical case:	Individual wears long sleeve shirt, pants, and shoes. The exposed skin surface is limited to the head and hands (2,000 cm^2);
Reasonable worst case:	Individual wears a short sleeve shirt, shorts, and shoes. The exposed skin surface is limited to the head, hands, forearms, and lower legs (5,300 cm^2).

For swimming and bathing scenarios, past exposure assessments have assumed that 75% to 100% of the skin surface is exposed (Vandeven and Herrinton, 1989; Wester and Maibach, 1989a). As shown in Table 8-3, total adult body surface areas can vary from about 17,000 cm^2 to 23,000 cm^2 or more. The mean is reported as about 20,000 cm^2. For default purposes, adult surface areas of 20,000cm^2 to 23,000 cm^2 are recommended. The defaults for children should be derived from Table 8-4 using the 50th and 95th percentile values for the ages of concern. Note that the values are slightly lower than those reported by EPA in 1985 but would not significantly affect the default values.

For soil contact scenarios, dermal exposure was expected to occur at the hands, legs, arms, neck, and head (McKone and Layton, 1986) with approximately 26% and 30% of the total surface area exposed for adults and children, respectively. Less conservative scenarios have limited exposure to the arms, hands, and feet. The clothing scenarios presented above, suggest that roughly 10% to 25% of the skin area may be exposed to soil. Since some studies have suggested that exposure can occur under clothing, the upper end of this range was selected for deriving defaults. Thus, applying 25% to the total body surface area results in defaults for adults of 5,000 cm^2 to 5800 cm^2. The defaults for children can be derived from multiplying the 50th and 95th percentiles by 0.25 for the ages of interest.

Table 8-3. Suface Area by Body Part for Adults (m^2)

	Men			Women		
Body Part	Mean (s.d.)	Min. - Max.	n	Mean (s.d.)	Min. - Max.	n
Head	0.118 (0.0160)	0.090 -0.161	29	0.110 (0.00625)	0.0953-0.127	54
Trunk	0.569 (0.0140)	0.306 -0.893	29	0.542 (0.712)	0.437 -0.867	54
Upper extremities	0.319 (0.0461)	0.169 -0.429	48	0.276 (0.0241)	0.215 -0.333	57
Arms	0.228 (0.374)	0.109 -0.292	32	0.210 (0.0129)	0.193 -0.235	13
Upper Arms	0.143 (0.0143)	0.122 -0.156	6	-	-	-
Forearms	0.114 (0.0127)	0.0945-0.136	6	-	-	-
Hands	0.084 (0.0127)	0.0596-0.113	32	0.0746 (0.00510)	0.0639-0.0824	12
Lower extremities	0.636 (0.0994)	0.283 -0.868	48	0.626 (0.0675)	0.492 -0.809	57
Legs	0.505 (0.0885)	0.221 -0.656	32	0.488 (0.0515)	0.423 -0.585	13
Thighs	0.198 (0.1470)	0.128 - 0.403	32	0.258 (0.0333)	0.258 -0.360	13
Lower legs	0.207 (0.0379)	0.093 -0.296	32	0.194 (0.0240)	0.165 -0.229	13
Feet	0.112 (0.0177)	0.0611-0.156	32	0.0975 (0.00903)	0.0834-0.115	13
TOTAL	1.94 (0.00374)[a]	1.66 -2.28[b]	48	1.69 (0.00374)[a]	1.45 -2.09[b]	58

[a] median (standard error)
[b] percentiles (5th - 95th)

s.d. = standard deviation.
s.e. = standard error for the 5th to 95th percentile of each body part.
n = number of observations

Source: Adapted from EPA (1985).

Table 8-4. Total Body Surface Area of Male Children in Square Meters

	Percentile								
Age (yr)[a]	5	10	15	25	50	75	85	90	95
2 < 3	0.527	0.544	0.552	0.569	0.603	0.629	0.643	0.661	0.682
3 < 4	0.585	0.606	0.620	0.636	0.664	0.700	0.719	0.729	0.764
4 < 5	0.633	0.658	0.673	0.689	0.731	0.771	0.796	0.809	0.845
5 < 6	0.692	0.721	0.732	0.746	0.793	0.840	0.864	0.895	0.918
6 < 7	0.757	0.788	0.809	0.821	0.866	0.915	0.957	1.01	1.06
7 < 8	0.794	0.832	0.848	0.877	0.936	0.993	1.01	1.06	1.11
8 < 9	0.836	0.897	0.914	0.932	1.00	1.06	1.12	1.17	1.24
9 < 10	0.932	0.966	0.988	1.00	1.07	1.13	1.16	1.25	1.29
10 < 11	1.01	1.04	1.06	1.10	1.18	1.28	1.35	1.40	1.48
11 < 12	1.00	1.06	1.12	1.16	1.23	1.40	1.47	1.53	1.60
12 < 13	1.11	1.13	1.20	1.25	1.34	1.47	1.52	1.62	1.76
13 < 14	1.20	1.24	1.27	1.30	1.47	1.62	1.67	1.75	1.81
14 < 15	1.33	1.39	1.45	1.51	1.61	1.73	1.78	1.84	1.91
15 < 16	1.45	1.49	1.52	1.60	1.70	1.79	1.84	1.90	2.02
16 < 17	1.55	1.59	1.61	1.66	1.76	1.87	1.98	2.03	2.16
17 < 18	1.54	1.56	1.62	1.69	1.80	1.91	1.96	2.03	2.09
3 < 6	0.616	0.636	0.649	0.673	0.728	0.785	0.817	0.842	0.876
6 < 9	0.787	0.814	0.834	0.866	0.931	1.01	1.05	1.09	1.14
9 < 12	0.972	1.00	1.02	1.07	1.16	1.28	1.36	1.42	1.52
12 < 15	1.19	1.24	1.27	1.32	1.49	1.64	1.73	1.77	1.85
15 < 18	1.50	1.55	1.59	1.65	1.75	1.86	1.94	2.01	2.11

[a] Lack of height measurements for children < 2 years in NHANES II precluded calculation of surface areas for this age group.

Source: EPA (1989a)

Assessors may want to refine estimates of surface area exposed on the basis of seasonal conditions. For example, in moderate climates, it may be reasonable to assume that 5% of the skin is exposed during the winter, 10% during the spring and fall, and 25% during the summer.

8.5. DERMAL ADHERENCE OF SOIL

8.5.1. Review of Experimental Data

A number of studies have attempted to determine the values of dermal soil adherence. Lepow et al. (1975) employed preweighed self-adhesive labels to sample a standard area on the palm of the hands. The preweighed labels were pressed on a single area, and often pressed several times on the given area to obtain an adequate sample. In the laboratory, labels were equilibrated in a desiccant cabinet for 24 hours (comparable to the preweighed desiccation), then the total weight was again recorded. The mean weight of hand dirt for the 22 hand samples was 11 mg; on a 21.5 cm^2 preweighed label, this amounts to 0.51 mg/cm^2. Lepow et al. (1975) stated that this amount (11 mg) represented only a small fraction (percent not specified) of the total amount of surface dirt present on the hands, since much of the dirt may be trapped in skin folds and creases; moreover, there may have been patchy distribution of the dirt on the hands.

Roels et al. (1980) assessed lead levels removed from children's hands by rinsing the hands in 500 mL dilute nitric acid. The amount of lead on the hands can be divided by the concentration of lead in soil to estimate the amount of soil adhering to the hands. The mean soil amount adhering to the hands was 0.159 g. Sedman (1989) used this estimate and the average surface area of the hand of an 11 year old (i.e., 307 cm^2) to estimate the amount of soil adhering per unit area of skin (0.9 mg/cm^2). The Sedman (1989) estimate assumed that approximately 60% (185 cm^2) of the lead on the hands was recovered by the method employed by Roels et al. (1980).

Que Hee et al. (1985) used soil having particle sizes ranging from 44 to 833 μm diameters, fractionated into six size ranges, to estimate the amount of soil adhering to skin. For each range of particle size, the amount of soil that adhered to the palm of the hand of a small adult was determined by applying approximately 5 g of soil for each size fraction, removing excess soil by shaking the hands, and then measuring the difference in weight before and after soil application. Several assumptions were made when the results were applied to other soil types and exposure scenarios. These assumptions include: (a) soil is composed of particles of the indicated diameters; (b) all soil types and particle sizes adhere to the skin to the degree observed in the study; and (c) an equivalent weight of particles of any diameter adhere to the same surface area of skin. On average, 31.2 mg of soil adhered to the small adult palm. The surface area of the palm of a small adult (approximately 14 years old with an average total body surface area of 16,000 cm^2 and a total hand surface area of 400 cm^2) is assumed to be approximately 160 cm^2. Based on these assumptions, 0.2 mg of soil adhered to 1 cm^2 of skin.

Sedman (1989) used the above estimates from Lepow et al. (1975), Roels et al. (1980), and Que Hee et al. (1985) to develop a maximum soil load that could occur on the skin given the types of procedures employed in each study to determine their measurements. A rounded arithmetic mean of 0.5 mg/cm^2 was calculated from the three studies. Sedman (1989) stated that this was near the maximum load of soil, and normally, it is unlikely that most skin surfaces would be covered with this great an amount of soil.

Driver et al. (1989) conducted soil adherence experiments which involved the use of various soil types collected from sites in Virginia. A total of five soil types were collected: Hyde, Chapanoke, Panorama, Jackland, and Montalto. Both top soils and subsoils were collected for each soil type. The soils were also characterized by cation exchange capacity, organic content, clay mineralogy, and particle size distribution. The soils were dry sieved to obtain particle sizes of $\leq$ 250 μm and $\leq$ 150 μm. For each soil type, the amount (mg) of soil adhering to adult male hands, using both sieved and unsieved soils, was determined gravimetrically (i.e., measuring the difference in soil sample weight before and after soil application to the hands). An attempt was made to measure only the minimal or "monolayer" of soil adhering to the hands. This was done by mixing a pre-weighed amount of soil over the entire surface area of the hands for a period of approximately 30 seconds, followed by removal of excess soil by gently rubbing the hands together after contact with the soil. Excess soil that was removed from the hands was collected and weighed with the original soil sample.

Driver et al. (1989) measured average adherences of 1.40 mg/cm^2 for particle sizes less than 150 μm, 0.95 mg/cm^2 for particle sizes less than 250 μm and 0.58 mg/cm^2 for unsieved soils. The analysis of variance statistics showed the most important factor affecting adherence variability was particle size, with a variance (F) ratio far in excess of the 0.999 significance value ($p < 0.001$). The next most important factor is soil type and subtype with an F ratio also in excess of 0.999 significance level ($p < 0.001$). The interaction of soil type and particle size was also significant, but at a lower 0.99 significance level ($p < 0.01$).

Driver et al. (1989) found statistically significant increases in adherence with decreasing particle size; whereas, Que Hee et al. (1985) found relatively small changes over particle size. Also, the amount of adherence found by Driver et al. (1989) was greater than that of Que Hee et al. (1985). Although it appears that soil particle size may affect adherence, exact quantitative relationships cannot be derived at this time because of insufficient data. It is suggested that this is an area for further study.

The U.S. EPA's Superfund Exposure Assessment Manual (EPA, 1988b) reported an upper-bound soil-to-skin adherence value of 2.77 mg/cm^2. This estimate was based on unpublished experiments by Dr. Rolf Hartung (University of Michigan) as reported in a 1979 memorandum from J. Harger to P. Cole (both from Michigan Toxic Substance Control Commission in Lansing, MI). According to this memo, Dr. Hartung measured adherence using his own hands and found: 2.77 mg/cm^2 for kaolin with a standard deviation (SD) of 0.66 and $N=6$, 1.45 mg/cm^2 for potting soil with $SD = 0.36$ and $N = 6$, and 3.44 mg/cm^2 for sieved vacuum cleaner dust (mesh 80) with $SD = 0.80$ and $N = 6$. The details of the experimental procedures were not reported. Considering the informality of the study and lack of procedural details, the reliability of these estimates cannot be evaluated. Accordingly, they were not included in the data summary presented in Table 8-5, nor were they considered in the selection of default values.

Table 8-5 summarizes the available soil adherence studies. The adherence value represents the amount of soil on the skin at the time of measurement. Assuming that the amount measured on the skin represents its accumulation between washings and that people wash at least once per day, then these adherence values could be interpreted as daily contact rates. However, since the residence time of soils on skin has not been studied (see above discussion) and since the adherence studies are independent of time, this is not recommended. Instead, it is recommended that these adherence values are interpreted on an event basis.

Table 8-5. Soil Adherence Values

Reference	Size Fraction (μm)	Soil Adherence (mg/cm^2)	Subjects
Lepow et al., 1975	–	0.5	humans
Roels et al., 1980	–	0.9 - 1.5	children
Que Hee et al., 1985[a]	< 44	0.17	children
	44-149	0.17	children
	149-177	0.19	children
	177-246	0.18	children
Driver et al., 1989[b]	< 150	1.40	human
	< 250	0.95	human
	unsieved	0.58	human
Yang et al., 1989[c]	< 150	9	rats

[a] Assume hand size = 160 cm^2.
[b] Five different soil types and 2-3 soil horizons.
[c] Rat skin "monolayer" (i.e., minimal amount of soil covering the skin).

The following analysis was used to review the data in Table 8-5 for purposes of recommending a default value. The soil adherence value from the Yang et al. (1989) study which used rat skin was not included for consideration because of the uncertainties associated with using this value for human dermal exposure scenarios. Among the remaining studies, the Lepow (1975) and the Roels (1980) studies have the advantage that they were conducted under actual field conditions and the disadvantage that they involved collection methods with unknown efficiencies. The use of collection methods that were less than 100% efficient suggest that the estimates may be low. However, only hand samples were collected which suggests that the estimates may be high for other parts of the body that probably have less soil contact. Finally, only children were surveyed, and they may not be representative of adults. The Que Hee et al. (1989) and Driver et al. (1989) studies used the gravimetric methods which do not involve a collection method with unknown efficiency and should, therefore, provide accurate estimates of adherence potential. However, these studies were conducted under laboratory conditions and examined adherence to hands only after intimate contact with soil. Such contact may not be representative of normal behavior. Parts of the body that have less intimate contact with the soil will likely have lower values. In summary, all studies have uncertainties which make it very difficult to recommend a default value. A range of values from 0.2 mg/cm^2 to 1.5 mg/cm^2 per event appear possible. Since this range is derived from hand measurements only, it may overestimate average adherence for the entire exposed skin area. Thus, the lower end of this range (0.2) may be the best value to represent an average over all exposed skin and 1 mg may be a reasonable upper value.

8.5.2. The Soil "Monolayer" Concept

Some investigators (Yang et al., 1989) have postulated that soil absorption occurs only from a "monolayer" of soil, and that the absorbed dose is independent of the amount of soil on the skin exceeding the monolayer. This monolayer has not been well defined but could be interpreted as a single layer of soil particles. Assuming tightly packed 100 μm particles, approximately 10,000 particles would fit on 1 cm^2 and weigh 8 mg/cm^2 (assuming particle density of 1,500 mg/cm^3). Since this value is higher than measured in all human skin adherence studies, it suggests that the adhered particles have an average diameter less than 100 μm or are not tightly packed.

Yang et al. (1989) attempted to measure a soil "monolayer" by covering the in vitro rat skin surface (which had been shaved) with a minimal amount of soil, then removing the excess soil by gently tapping the inverted diffusion cell and weighing the excess. This procedure indicated that 9 mg/cm^2 adhered to the rat skin. Yang et al. (1989) found a lower percentage absorption from a thick soil layer (56 mg/cm^2) compared to a "monolayer" (9 mg/cm^2), with 1.3% and 8.4% of benzo[a]pyrene (BaP) absorbed in 96 hours, respectively, from each type of soil, even though both soil doses contained about 1 ppm of BaP in the soil. However, nearly identical quantities of benzo[a]pyrene (1.3 ng) were absorbed from the thick layer and the "monolayer" of soil. The constant amount of BaP absorbed from soil over the 96 hour testing period, regardless of the amount of soil applied, led Yang et al. (1989) to conclude that the small amount of BaP absorbed was entirely derived from the "monolayer" of soil in direct contact with the skin.

Yang et al. (1989) also conducted exploratory in vitro experiments to assess the minimum amount of soil that would adhere to the shaved rat skin. Close examination of skin sections after removal of excess soil indicated that the components remaining on the skin were predominantly silt and clay fractions (<50 μm particle size). This fine fraction contains the bulk of the soil organic carbon content, which is the dominant sorbent for lipophilic compounds. Thus, clay and silt are more effective sorbents than sand. Yang et al. (1989) carried out the percutaneous absorption experiments exclusively with soil particles of <150 μm, and approximately 9 mg/cm^2 of soil (which was found to be the minimum amount required for a "monolayer" coverage of rat skin in both in vitro and in vivo tests). This value was acknowledged to be higher than the minimal amounts of soil (monolayer) tested by Driver et al. (1989) with human skin (Table 8-5). Yang et al. (1989) stated that the differences between rat and human soil adherence findings may be a result of differences between rat and human skin texture, the types of soils tested, soil moisture contents, or possibly the methods of measuring soil adhesion.

In summary, the monolayer concept may affect how to interpret and study soil adherence on skin in the future. Currently, however, it is not sufficiently well understood to incorporate into soil adherence estimates. Chapter 6 presents further discussion of this issue.

8.6. METHODS FOR MEASURING DERMAL EXPOSURE

The direct assessment of dermal exposure is accomplished by measuring the concentration or amount of the contaminant in contact with the skin over a period of time. The methods developed for such purposes have evolved from industrial hygiene practices and, generally, entail either the removal of accumulated residues from the skin or collection of the material as contact occurs. The removal methods include uncertainties in the removal efficiency and require that the duration of contact be evaluated through independent means. Uncertainty is introduced by the collection methods through the use of materials that usually do not mimic the adherence characteristics of the skin accurately. These methods are summarized briefly below:

Removal Procedures:

- Rinse Method - Various solvents can be used to rinse the exposed skin and remove residues. These solvents are then analyzed for the contaminant of interest. Roels et al. (1980) used a dilute nitric acid rinse to measure lead levels on skin.

- Wipe Method - Solvent impregnated materials can be used to wipe the skin and remove residues. The wipe material is then analyzed for the contaminants of concern.

- Tape Method - Adhesive tape can be applied to the skin for purposes of removing contaminant residues. A gravimetric procedure is used to estimate the amount of residue removed with the tape. Lepow et al. (1975) used this procedure to measure soil levels on skin.

Collection Procedures:

- Patch Method - Patches made of various materials can be placed on the body to collect contaminants of interest as contact occurs. The patches are designed to have adherence characteristics similar to skin. This technique was developed about 30 years ago to investigate the source of intoxication among handlers of organophosphates (Durham and Wolfe, 1962). The method requires some fairly extensive assumptions, and in the occupational setting, it has proven to be useful for screening purposes but is limited as a quantitative method.

- Glove Method - Absorbent gloves can be used to collect contaminants contacting the hands. This method has been used to measure hand exposure to pesticides resulting from use of household sprays and flea shampoos for pets (EPA, 1990f).

- Whole Body Dosimetry - This method involves the use of clothing covering the whole body (usually cotton, long underwear tops and bottoms and socks) to trap contaminants (EPA, 1986). A problem with this method is the difficulty in extracting residues from such a large collector. An advantage of this method over the patch method is that it is less likely to miss areas where exposure may occur.

Other Procedures:

- Fluorescent Tracers - This procedure involves treating the contaminant of concern with a nontoxic fluorescent tracer and then using video imaging to identify and quantify the points where the contaminant contacts the skin (Fenske et al., 1985, 1986).

8.7. SUMMARY AND CONCLUSIONS

This chapter has reviewed the available data on parameters needed to characterize dermal contact scenarios involving water and soil. For each parameter, a range of default values were derived corresponding to central- and upper-end values. These values are summarized below in Table 8-6.

Table 8-6. Range of Recommended Defaults for Dermal Exposure Factors

	Water Contact				Soil Contact	
	Bathing		Swimming			
	Central	Upper	Central	Upper	Central	Upper
Event time and frequency	10 min /event 1 event/day 350 days/yr	15 min /event 1 event/day 350 days/yr	0.5 hr/event 1 event/day 5 days/yr	1.0 hr /event 1 event /day 150 days /yr	40 events/yr	350 events/yr
Exposure duration	9 yr	30 years	9 yr	30 years	9 yr	30 years
Adult skin surface area (See Table 8-3 for children)	20,000 cm^2	23,000 cm^2	20,000 cm^2	23,000 cm^2	5000 cm^2	5,800cm^2
Soil-to-skin adherence rate					0.2 mg/cm^2-event	1.0 mg/cm^2-event

Additionally, the methods for direct measurement of dermal exposure were summarized. These methods consisted primarily of procedures for removing residues on the skin or collecting contaminants as the contact occurs.

In summary, the supporting data are weak for several dermal exposure factors. Therefore, research is strongly recommended in the following areas:

- Soil adherence levels, especially levels found on parts of bodies other than hands during normal soil contact activities;
- Influence of moisture content and other soil properties on adherence to skin;
- Residence time of soil residues on skin;
- Soil contact frequency, especially as a function of age, location, activity, climate, etc.; and
- Swimming event times and frequencies.

9. RELATIVE CONTRIBUTION OF DERMAL EXPOSURE TO TOTAL ABSORBED DOSE

For purposes of scoping and planning an exposure and risk assessment, it is useful to know when it is important to consider dermal exposure pathways. Assessors must decide what level (from cursory to detailed) of analysis is needed to make this decision. This chapter addresses this issue primarily by analyzing when the dermal exposure route is likely to be significant when compared to the other routes of exposure. The chapter begins with some general considerations regarding this issue and then presents sections on media specific considerations, i.e., compounds in neat form, in water, in air, and in soil.

9.1. GENERAL CONSIDERATIONS FOR DETERMINING IMPORTANCE OF DERMAL ROUTE

In order to illustrate the general procedure to decide whether dermal exposure is likely to be a significant route of exposure, a decision matrix has been developed to assist the assessor (Figure 9-1). This decision matrix was developed by comparing the following scenarios:

- For water contact: adults drinking 2 L water/day compared to showering 10 minutes/day with surface area exposed equal to 20,000 cm^2
- For soil contact: adults ingesting 100 mg soil/day compared to dermal exposure of 1 mg soil/cm^2, with surface area exposed equal to 5,000 cm^2

As shown in Figure 9-1, the first step is to identify the chemical of concern. The next step is to make a preliminary analysis of the chemical's environmental fate and the population behavior to judge whether dermal contact may occur. The third step is to review the dermal toxicity of the compound and determine if it can cause acute effects. As explained in the Introduction to this document (Chapter 1), the scope of this effort has been limited to dermal exposure assessments in support of risk assessments for systemic chronic health effects. However, consideration of other types of health effects can be a critical factor in determining the overall importance of the dermal exposure route. Even if the amount of a compound contacting the skin is small compared to the amount ingested or inhaled, the dermal route can still be very important to consider for compounds that are acutely toxic to the skin. Therefore, a brief discussion is provided here with references to

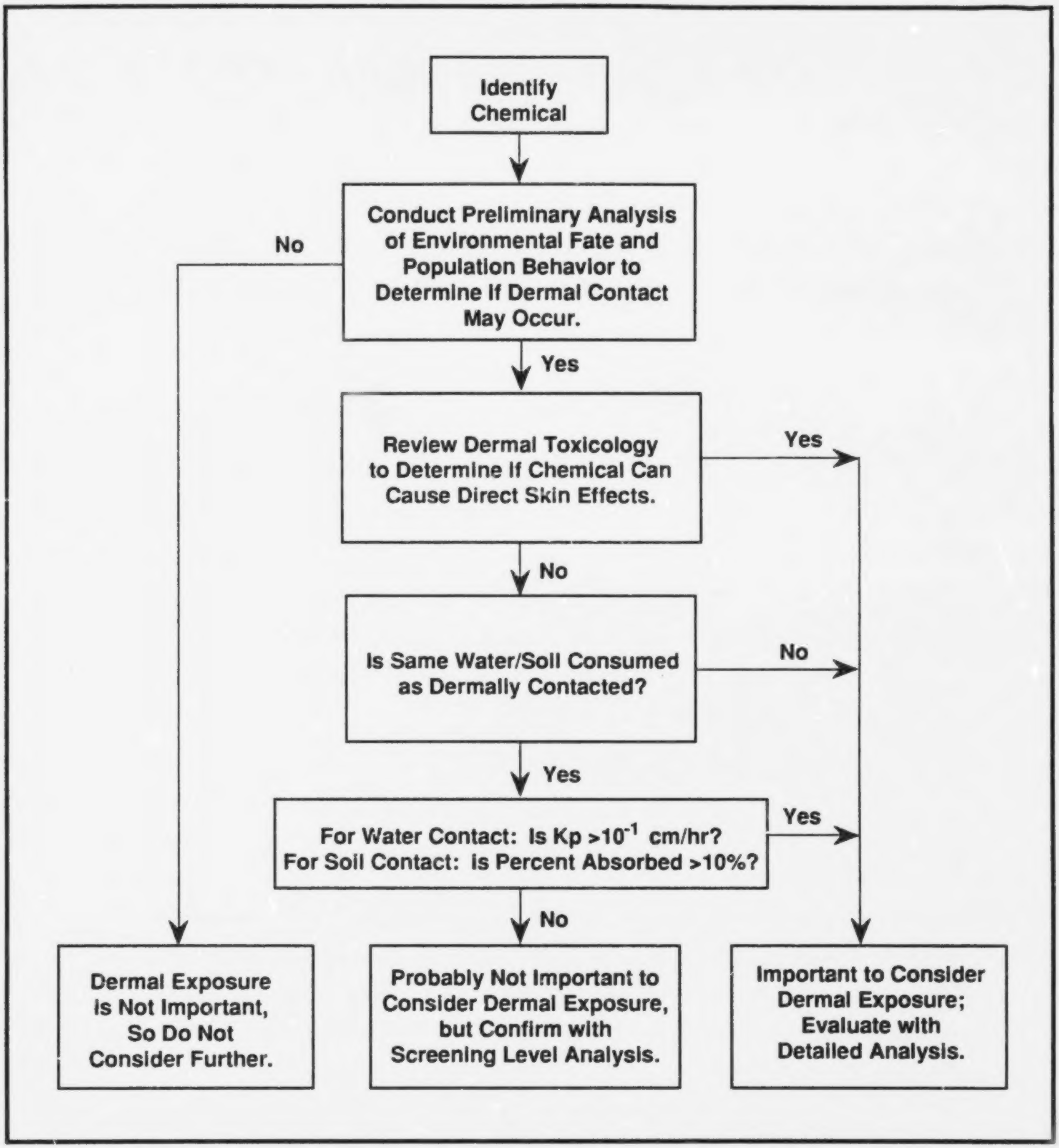
Identify Chemical
Conduct Preliminary Analysis of Environmental Fate and Population Behavior to Determine If Dermal Contact May Occur.
No
Yes
Review Dermal Toxicology to Determine If Chemical Can Cause Direct Skin Effects.
Yes
No
Is Same Water/Soil Consumed as Dermally Contacted?
No
Yes
For Water Contact: Is Kp >10^{-1} cm/hr? For Soil Contact: Is Percent Absorbed >10%?
Yes
No
Dermal Exposure Is Not Important, So Do Not Consider Further.
Probably Not Important to Consider Dermal Exposure, but Confirm with Screening Level Analysis.
Important to Consider Dermal Exposure; Evaluate with Detailed Analysis.

Figure 9-1. Decision matrix to evaluate importance of dermal exposure.

other documents for further details. Some obvious classes of compounds that cause direct irritation are strong acids and bases. Lead, mercury, and chromium are well known skin sensitizers and can cause irritation at low concentrations. Additional information on compounds (and associated concentrations) that cause skin irritation and sensitization are available in the following references:

- Merck Index (1989)
- Patty's Industrial Hygiene and Toxicology (1978)
- Material Safety Data Sheets (supplied by the manufacturer for each chemical)
- Occupational Health Guidelines published by the U.S. Department of Health and Human Services (1983)
- U.S. Department of Transportation's Emergency Response Guidebook (DOT, 1990)
- Permissible Exposure Limits of the Occupational Safety and Health Administration (OSHA) (1990)
- Threshold Limit Values published by the American Conference of Governmental Industrial Hygienists (ACGIH) (1990-91)
- Occupational Diseases of the Skin (Schwartz et al., 1957)
- Dermatotoxicology (Marzulli and Maibach, 1991)
- Contact Dermatitis (Fisher, 1967)

The remainder of this procedure evaluates the importance of dermal contact by comparing it to other exposure routes that are likely to occur concurrently. For example, the importance of dermal contact with water is evaluated by assuming that the same water is used for drinking purposes as for swimming or bathing and comparing these two pathways. Similarly the importance of dermal contact with soil is evaluated by assuming that the same soil is involved in direct ingestion as dermal contact and comparing these two pathways. However, the underlying assumption that concurrent exposure routes will occur is not valid in all situations. For example, the water in a contaminated quarry may not be used as a domestic water supply but may be used for occasional recreational swimming. Even where concurrent exposure routes occur, the contaminant concentrations may differ. For example, in a situation involving a contaminated river used as a domestic water supply, swimmers may be exposed to a higher concentration in the river than occurs during ingestion of tap water due to treatment. Thus, the assessor should confirm the assumptions that concurrent exposures occur and that the same contaminant levels apply. Where these assumptions are not valid, dermal exposure should be evaluated independently.

The final step shown in Figure 9-1 is to review the dermal absorption properties of the compound to determine whether an absorbed dose of concern may occur. The actual assessment for the scenarios under comparison are discussed in Section 9.3. and Section 9.5. As is shown in Section 9.3., dermal exposure to compounds in water (from 10 minutes showering/day) with a permeability coefficient greater than 10^{-1} cm/hour may pose risks similar to or greater than direct ingestion of 2 L water/day. This value is recommended as a preliminary indicator of when contact with water may be a concern. As is discussed in Section 9.5., for adults, dermal contact with soil generally appears to be a concern relative to direct ingestion when the percent absorbed exceeds 10%. The development of similar recommendations for contact with vapors or neat compounds was beyond the scope of this effort.

On the basis of the last step, either a screening level or in-depth analysis is recommended. A screening level analysis involves estimating the amount of contaminant that may be contacted and the resulting absorbed dose using the procedures and default values provided in Chapter 10. Contaminant concentrations should be estimated using simple fate models to compute long-term averages or simply making worst-case assumptions. An in-depth analysis involves developing a more complete description of the anticipated skin exposure and the conditions of that exposure. At a minimum, the steps in Chapter 10 should be followed trying to use site-specific conditions to fine-tune estimates of parameter values rather than the defaults. Where dermal exposure to children is possible, the summation approach should be used to account for changes in surface area and body weight (see Chapter 10). More precise estimates of contaminant concentrations and how they change over time should be developed using more complex fate models or more extensive monitoring. Ideally, even more sophisticated procedures are needed to fully evaluate dermal exposure where it may be an important concern. Although beyond the scope of this document, some additional considerations for such an advanced assessment are described as follows:

- The assessor should determine whether the exposure is continuous or intermittent, the time of each exposure event, the duration of each exposure event, and the frequency of exposure. For instance, a significant difference would be observed between a continuous

5-minute exposure to a compound like xylene, compared to ten 30-second exposures with rinsing, evaporation, or washing in between the exposures. Proper consideration of these factors would involve the use of pharmacokinetic models.

- The assessor should consider the temperature of the contacted material. High temperatures may change permeability characteristics of a compound or reduce contact with volatiles in water.

- The assessor should consider loss from the skin by cleansing, evaporation, wiping, sorption by clothing or toweling, or cleansing with soap or surfactant solutions.

9.2. CONTRIBUTION OF DERMAL EXPOSURE TO THE TOTAL ABSORBED DOSE OF NEAT COMPOUNDS

Engstrom et al. (1977) determined that immersion of both hands in liquid xylene for 15 minutes would result in the systemic absorption of 35 mg of this compound. Based on previous data, these investigators estimated that inhalation of xylene at 100 ppm for the same period (15 minutes) would result in the absorption of about 40 mg of xylene (60% retention of 10 L/minute ventilation). Although it is unlikely that continuous dermal exposure to liquid xylene would occur over a 15-minute period in the workplace, it is not unreasonable to expect that intermittent topical application of this solvent, or exposure to aqueous solution of xylene, would occur over the same period.

Guest et al. (1984) compared pulmonary and percutaneous absorption of 2-propoxyethyl acetate (PEA) or 2-ethoxyethyl acetate (EEA) in beagle dogs. The dogs were exposed to 50 ppm of either compound (299 mg/m^3 of PEA and 270 mg/m^3 of EEA) for 300 minutes with breath samples taken periodically both during and after exposure. From these data, Guest et al. (1984) estimated a pulmonary absorption rate of 74% of inhaled PEA and 68% of inhaled EEA. Percutaneous absorption rates (fluxes) were measured both in vivo and in vitro in beagle dogs by applying an excess amount of neat compound. In vivo absorption rates for PEA, calculated for exposure periods of 30 and 60 minutes, were 1.2 mg/cm^2-hour and 0.8 mg/cm^2-hour, respectively. In vivo absorption rates for EEA, calculated for exposure periods of 30 and 60 minutes, were 1.7 mg/cm^2-hour and 0.8 mg/cm^2-hour, respectively. In vitro absorption rates, calculated under steady-state conditions, were 2.3 mg/cm^2-hour for EEA and 1.5 mg/cm^2-hour for PEA. Guest et al. (1984) used the absorption data obtained in vivo in the dog to estimate absorbed dose in humans exposed via the pulmonary route to 50 ppm of PEA or EEA for 1 hour and via the dermal route to the neat compounds in contact with both hands for 0.5 or 1 hour. Using these assumptions, the dose absorbed via the skin was estimated to be three to four times greater than the dose absorbed via the respiratory tract, as shown in Table 9-1.

Table 9-1. Estimation of PEA and EEA Uptake in Man

Route of Exposure	Exposure Time (hr)	Estimated Uptake (mg) PEA	Estimated Uptake (mg) EEA
Inhalation (50 ppm)[a]	1.0	270	220
Skin (hands)[b]	0.5 to 1.0	580 to 760	640 to 645

[a] 1.25 m^3 air inhaled per hour; absorption; 74% (PEA) or 68% (EEA).

[b] 175 cm tall human, surface area 1.85 m^2; hands comprise 4% surface area, human dermal uptake comparable to uptakes measured in vivo in beagles; dermal uptake of PEA of 1.2 mg/cm^2-hour for exposures of 0.5 hour and 0.8 mg/cm^2-hour for exposure of 1 hour; dermal uptake of EEA of 1.7 mg/cm^2-hour for exposure of 0.5 hour and 0.8 mg/cm^2-hour for exposure of 1 hour.

Source: Guest et al. (1984)

The studies conducted by Engstrom et al. (1977) and Guest et al. (1984) are two examples of how dermal exposure serves as a significant route of exposure to neat organic compounds

9.3. CONTRIBUTION OF DERMAL EXPOSURE TO THE TOTAL ABSORBED DOSE OF COMPOUNDS IN AQUEOUS MEDIA

Brown et al. (1984) demonstrated the importance of dermal exposure, relative to oral absorption for the uptake of VOCs from drinking water. Using the fluxes from aqueous solutions reported by Dutkiewicz and Tyras (1967, 1968), Brown et al. (1984) used Fick's first law to calculate average K_p values for toluene, ethylbenzene, and styrene. These K_p values were then used in the following equation[1] to calculate absorbed dose via the dermal route:

$$\text{Dermal Dose} = [\text{Permeability constant } \left(\frac{L}{cm^2 \times hr}\right) \times \text{duration of exposure } (hr) \times \text{total body surface area } \left(cm^2\right) \times \text{fraction of body surface area exposed} \times \text{concentration } \left(\frac{mg}{L}\right)] \div \text{body weight } (kg) \qquad (9.1)$$

Oral doses of these compounds from the consumption of drinking water were obtained by:

$$\text{Oral Dose} = \frac{\text{concentration } (mg/L) \times \text{amount consumed } (L/day)}{\text{body weight } (kg)} \qquad (9.2)$$

Brown et al. (1984) then proposed three scenarios in which the estimated oral and dermal doses were compared:

Scenario 1:	70 kg adult bathing 15 minutes, 80% immersed (skin absorption), 2L water consumed per day (ingestion), 18,000 cm^2 body surface area.
Scenario 2:	10.5 kg infant bathed 15 minutes, 75% immersed (skin absorption), 1L water consumed per day (ingestion), 4,000 cm^2 body surface area.
Scenario 3:	21.9 kg child swimming 1 hour, 90% immersed (skin absorption), 1L water consumed per day (ingestion), 8,800 cm^2 body surface area.

---

[1] This equation is taken directly from Brown et al. (1984). According to the context of Brown et al. (1984), the hours in the units of the permeability constant are in the denominator; if the equation were written in the units used in this Interim Guidance report, K_p would be in units of cm/hour, arrived at by multiplying the Brown et al. (1984) permeability constant in L/(cm^2 x hr) by a conversion factor of 1,000 cm^3/L. Also, the body surface area exposed should be a decimal fraction, rather than a percent.

The estimated contribution of each route of exposure for each scenario is presented in Table 9-2. In these scenarios, dermal exposure contributes significantly to the estimated dose of these compounds from drinking water, even when the gastrointestinal absorption efficiency was assumed to be 100% (note that the respiratory exposure is ignored in these computations and scenarios).

By examining Equations 9-1 and 9-2, one can evaluate the factors that lead to increased dermal absorption relative to ingestion. Since the concentration of the chemical in water and the body weight of the exposed individual appear in both Equations 9-1 and 9-2, the relative quantities absorbed via each route should remain the same when either or both of these factors are changed. Increasing the duration of dermal exposure will increase the contribution of dermal exposure relative to ingestion as components of the total dose via the dermal and ingestion routes of exposure. As shown in Scenario 3 of Table 9-2, a child swimming for 1 hour in water containing 5 ppb to 0.5 ppm concentrations of three compounds will dermally absorb 6 to 10 times the amount of the compound relative to the amount that would be absorbed orally after ingestion of 1L of drinking water with the same concentrations of chemical contaminant (even assuming 100% oral uptake). Scenario 3 has a dermal contact time of 1 hour, while Scenarios 1 and 2 represent only 15 minutes dermal contact, and this increase in exposure duration contributes to the increases in relative contribution of dermal exposure as shown in Table 9-2.

Table 9-2 is essentially verbatim from Brown et al. (1984) who also presented the estimated dose data in mg/kg. The percentages for each chemical within each scenario should be exactly the same, but Brown et al. (1984) had computed the percentages from their calculated dermal and oral doses. Their estimated dermal and oral doses had been rounded to two or only one significant figure; hence, the percentages within scenarios for each of the chemicals are artificially different. Table 9-2 shows the Brown et al. (1984) values, as well as unrounded, recalculated values in parentheses.

In Table 9-2, note that the concentration of pollutant in water varies over a 100-fold range, but has little impact on the contribution of dermal vs. oral exposure relative to total dose. The larger the K_p, the larger the contribution of dermal exposure to total absorbed dose; for example, toluene with a K_p of 0.001 L/cm^2-hour (1.0 cm/hour) showed slightly higher dermal exposures than ethylbenzene with a K_p of 0.00095 L/cm^2-hour (0.95 cm/hour) which was even larger still than styrene with a K_p of 0.00065 L/cm^2-hr (0.65 cm/hour). Increasing the surface area of skin exposed will increase the contribution of dermal exposure to total exposure; while increasing the ingestion rate of water will increase the contribution of ingestion. The effect of changing the surface area or the ingestion rate is not as clearly illustrated by the Brown et al. (1984) scenarios as the effects of changing exposure duration and K_p. Surface area exposed and ingestion rate would be more important factors if they varied over wider ranges than those of the Brown et al. (1984) scenario.

Table 9-2. Relative Contribution (%) of Dermal and Oral Exposure to Dose

Compound[a]	Concentration (mg/L)	Scenario 1[b]		Scenario 2		Scenario 3	
		Dermal	Oral	Dermal	Oral	Dermal	Oral
Toluene	0.005	67 (65)	33 (35)	44 (43)	56 (57)	91 (89)	9 (11)
	0.10	63 (65)	37 (35)	46 (43)	54 (57)	89 (89)	11 (11)
	0.5	59 (65)	41 (35)	45 (43)	55 (57)	89 (89)	11 (11)
Ethylbenzene	0.005	75 (63)	25 (37)	44 (42)	56 (58)	91 (88)	9 (12)
	0.10	63 (63)	37 (37)	46 (42)	54 (58)	89 (88)	11 (12)
	0.5	68 (63)	32 (37)	45 (42)	55 (58)	89 (88)	11 (12)
Styrene	0.005	67 (54)	33 (46)	29 (33)	71 (67)	83 (84)	17 (16)
	0.10	50 (54)	50 (46)	35 (33)	65 (67)	84 (84)	16 (16)
	0.5	59 (54)	41 (46)	29 (33)	71 (67)	83 (84)	17 (16)

[a] Permeability coefficients calculated by Brown et al. (1984) as follows:
toluene = 0.001 L/cm^2-hour (1 cm/hour);
ethylbenzene = 0.00095 L/cm^2-hour (0.95 cm/hour); and
styrene = 0.00065 L/cm^2-hour (0.65 cm/hour).

[b] Numbers in parentheses are recalculated percentages, because Brown et al. (1984) had rounded their estimated doses prior to calculating the relative contribution percentages.

Source: Brown et al. (1984)

Several investigators (EPA, 1984c; Shehata, 1985; McKone, 1987) have shown that the respiratory route can contribute significantly to the total body burden of VOCs that volatilize from drinking water. Using an indoor air quality model developed by Wadden and Scheff (1983), Shehata (1985) estimated the amount of benzene, toluene, and xylene introduced into indoor air from drinking water sources (i.e., baths, showers, toilets, dishwashers, washing machines, and boiling water and other cooking). This information was used to estimate the dose of each compound absorbed via the respiratory tract by occupants exposed to these pollutants in a "typical" house. The relative contribution of each route of exposure was then estimated using the assumptions listed in Table 9-3.

Table 9-3. Absorption Constants (Fraction Absorbed) for Various Routes of Exposure

Chemical	Inhalation (%)	Oral (%)	Dermal (L/cm^2 x hr)
Benzene	50.0	100.0	2.0×10^{-5}
Toluene	93.0	100.0	9.5×10^{-4}
Xylene	64.0	100.0	3.8×10^{-4}

Source: Shehata (1985)

The inhalation dose was calculated by:

$$\textit{Inhalation dose (mg)} = \textit{Indoor air concentration } (mg/m^3) \times \textit{daily respiratory rate } (m^3/day) \times \textit{fraction absorbed} \tag{9.3}$$

The method used to calculate the oral dose was similar to that used by Brown et al. (1984), with an additional term to account for ingestion of the pollutant through food consumption. It was stated in Shehata (1985) that the dermal K_p values for benzene and toluene were taken from the Brown et al. (1984) study; however, benzene was not one of the chemicals reported on by Brown et al. (1984). Also, the xylene K_p was "extrapolated" by Shehata (1985), but it is unclear how this value was determined. The relative contribution of each route of exposure to the total daily dose of each compound for a child in one exposure scenario (that is, one living in a rural area in the summer) is presented in Table 9-4.

The concentration of the compound in drinking water has no effect on the relative contribution of dermal exposure. Of the three compounds presented in Table 9-4, dermal absorbed dose of toluene (the compound with the highest estimated K_p) contributes more to total absorbed dose than dermal absorbed dose of benzene or xylene. The findings from Shehata (1985) suggest dermal exposure is less important than those estimates from other studies, but considering the uncertainties in the approach, these findings cannot be fully evaluated.

Table 9-4. Effect of Drinking Water Concentration on Relative Exposure Via All Routes to a Child's Total Body Burden in Summer (Rural)[a]

Chemical	Drinking Water Concentration (mg/L)	Percent Relative Contribution		
		Inhalation	Oral	Dermal
Benzene	0.0	0.0	100.0	0.0
	0.005	1.0	99.0	0.0
	0.05	5.0	95.0	0.0
	0.5	15.0	84.0	1.0
	5.0	20.0	79.0	1.0
	50.0	20.0	78.0	1.0
Toluene	0.0	0.0	0.0	0.0
	0.005 - 50.0[b]	22.0	45.0	32.0
Xylene	0.0	0.0	0.0	0.0
	0.005 - 50.0[b]	21.0	62.0	18.0

[a] The assessment includes all identified pathways of exposure (not just drinking water), and includes contributions of the chemical from food. That is why the oral route contributes 100% to the exposure for benzene when there is 0.0 mg/L benzene in the drinking water.

[b] The same percent relative contribution was reported at 0.005, 0.05, 0.5, 5.0, and 50.0 mg/L.

Source: Shehata (1985)

Hall et al. (1989) used the concept of pathway-exposure factors, expressed in units of (mg/kg-day)/(mg/L), to compare the relative contribution of oral, respiratory, and dermal pathways to the percent of the lifetime equivalent exposure to trans-1,2-dichloroethylene attributable to each of the three pathways (Table 9-5).

Table 9-5. Lifetime Equivalent Exposure Factors (Expressed as Percent of Total Exposure) for Trans-1,2-Dichloroethylene in Tap Water

	Fluid Ingestion	Indoor Inhalation	Dermal Absorption
Best Estimate	31	41	28
Upper Bound	21	65	14

Source: Hall et al. (1989)

Hall et al. (1989) developed their model such that the pathway exposure factor, F, is used to translate the water-supply concentration, C_w in mg/L, into the total equivalent average lifetime exposure, DAD in mg/kg-day, as follows:

$$DAD\ (mg/kg\text{-}day) = F\ (L/kg\text{-}day)\ x\ C_w\ (mg/L) \tag{9.4}$$

For each of the three pathways (i.e., water ingestion, inhalation, dermal absorption), the equivalent lifetime exposure within a population is composed of three age categories. The overall exposure factors, F, are calculated as the weighted sum of the pathway-exposure factors, f (age group), for each of the three age categories:

$$F = \frac{2}{70}\ f\ (infant) + \frac{14}{70}\ f\ (child) + \frac{54}{70}\ f\ (adult) \tag{9.5}$$

where 2/70, 14/70, and 54/70 reflect the fraction of time (in years) that each population cohort spends in each age category. For the water ingestion pathway, the intake values per unit body weight were 0.11 and 0.044 L/kg-day for the infant and child, respectively. For adults, the fluid intakes were bracketed using the adult average fluid intake of 1.4 L/day for a 60 kg female (0.023 L/kg-day) and 2.0 L/day for a 73 kg male (0.027 L/kg-day) for a "best-estimate" average of 0.025 L/kg-day. For the "upper bound" average, the moderately active adult average intake was taken to be 3.7 L/day for 65.5 kg average adult, 0.056 L/kg-day. Thus, the overall weighted sum of the water ingestion pathway was 0.031 L/kg-day for the best estimate and 0.055 L/kg-day for the upper bound.

Indoor inhalation values are calculated according to the indoor air model for VOCs developed by McKone (1987). The assumptions listed in Hall et al. (1989) include that the typical household has four occupants and uses 900 L/day of water contaminated with 1 mg/L of trans-1,2-dichloroethylene. The time-dependent concentration profile in shower stall, bathroom, and household air, and the resulting effective lifetime doses were derived using the McKone (1987) model, and Hall et al. (1989) used an almost identically verbatim set of assumptions as appears in McKone (1987). The approach resulted in estimated inhalation pathway-exposure factors of 0.041 L/kg-day for typical households (best estimate) and 0.17 L/kg-day for the upper-bound estimate.

For the dermal route, Hall et al. (1989) assumed dermal exposure occurred only during bathing and showering, and made the following simple assumptions:

- Resistance to diffusive flux through layers other than the stratum corneum is negligible;
- Steady-state diffusive flux is proportional to the concentration difference between the skin surface and internal body water;
- An adult spends from 10 to 20 minutes in a bath or shower each day;
- During bathing, roughly 80% of the skin is in contact with water, and during showers, roughly 40% of the skin is in contact with water; and
- Children and infants spend approximately 1 hour/week in bathing or swimming.

The dose absorbed per event, M, from dermal absorption is given by the expression:

$$M = J_{ss}\, t_{event}\, f_s\, A_t \qquad (9.6)$$

where:

M = Dose absorbed per event (mg/event)

J_{ss} = Steady-state flux across the stratum corneum (mg/cm^2-hr)
t_{event} = Duration in the shower or bath (hr/event)
f_s = Fraction of the skin surface in contact with water (unitless)
A_t = Total surface area of the skin (cm^2)

This dose equation and the Fick's first law equation are used to obtain lifetime equivalent exposure factors for dermal absorption using a weighted sum approach comparable to that used for ingestion for the three age groups. The best estimate approach, assuming a 10-minute bath for adults, yielded a pathway exposure factor of 0.028 L/kg-day; and the higher (upper-bound) estimate assumed a 20-minute bath for adults and yielded a pathway exposure factor of 0.037 L/kg-day.

In the very typical, "best estimate" scenario, each exposure pathway contributes about equal amounts of 1,2-dichloroethylene to the total dose, with a range of 28% to 41% of the total. In a reasonable approximation of more extensive exposure, the relative contribution of dermal exposure to the total dose of 1,2-dichloroethylene decreases, but the dermal contribution remains similar to the dose received via ingestion of drinking water, with 14% and 21% of the total, respectively.

Each of the previous calculations of absorbed dose were based on the assumption that a steady-state rate of dermal uptake was occurring. However, Brown and Hattis (1989) pointed out that their previous use of this assumption (Brown et al., 1984) may be invalid for the relatively brief exposure periods of 15 to 20 minutes bathing as encountered in typical exposure scenarios. Brown and Hattis (1989) re-examined the data from their earlier study (Brown et al., 1984) relative to this issue for ethylbenzene, toluene, and styrene and reported estimated doses for 60-minute exposures which were greater than the doses in Brown et al. (1984). Also included in Brown and Hattis (1989) were estimates shown in Table 9-6 using a pharmacokinetic model to estimate the dermal absorption of VOCs (ethylbenzene, tetrachloroethylene, and trichloroethylene) from aqueous solutions. Using this approach, Brown and Hattis (1989) estimated a "minimum" and "maximum" adult daily dose of three VOCs in drinking water received via dermal absorption and compared these doses to those expected from oral and respiratory uptake. The oral dose values were obtained by assuming an intake of 2L of drinking water/day. The inhalation dose was based on the model of McKone (1987). The relative contribution of each route to daily dose is presented in Table 9-6. Only one compound, ethylbenzene, had a dermal uptake as large as uptake by inhalation and ingestion when conditions were set to allow for maximal dermal absorption; for the maximum concentration exposure scenarios, the dermal percents of total daily dose were less for both tetrachloroethylene and trichloroethylene, but were about one-third and about one-half the contributions of respiratory and oral exposures, respectively, as percents of the total daily dose.

Table 9-6. Relative Contribution of Different Routes of Exposure to the Absorbed Dose of VOCs in Drinking Water

	Percent of Total Dose			
	Oral	Respiratory	Dermal	
Ethylbenzene	37.9	54.5	7.6	Min[a]
	26.0	37.3	36.7	Max
Tetrachloroethylene	41.7	56.9	1.5	Min
	34.3	46.8	18.9	Max
Trichloroethylene	40.6	58.2	1.2	Min
	34.3	49.2	16.5	Max

[a] Hypothetical conditions that result in a "minimum" or "maximum" amount of the compound being absorbed (see text).

Source: Adapted from Brown and Hattis (1989)

The parameters changed by Brown and Hattis (1989) to reflect these "minimum" and "maximum" conditions of dermal uptake include physiological and anatomical factors, such as percentage of skin fat, and percentage of blood fat (Table 9-7). These two parameters may affect the skin/blood partitioning of the compounds. Curiously, the skin thickness value was also increased by Brown and Hattis (1989) under "maximum" uptake conditions. The parameter that was varied to the greatest extent by Brown and Hattis (1989) was a unitless empirical constant. This constant (CONST) was incorporated into the dermal absorption equation to account for the various uncertainties in estimating the other parameters of the dermal absorption rate equation, including the stratum corneum/water partition coefficient ($K_{sc/w}$), diffusion coefficient (D_s), surface area of exposed skin, and thickness of the stratum corneum, as well as to account for deviations from Fick's first law. Therefore, it is probably accurate to represent the different doses as occurring at "maximum" or

Table 9-7. Assumed Minimum and Maximum Conditions for Dermal Absorption as Defined by Brown and Hattis (1989)

Parameter	Minimum	Maximum
Constant	1	20
Skin Thickness (cm)	0.02	0.1
Skin Fat (%)	2.5	2.0
Blood Fat (%)	2.7	0.9

"minimum" levels of uncertainty. Whatever its meaning, increasing the value of this parameter (CONST) effectively increases the rate of dermal absorption. This comparison of the Brown and Hattis (1989) estimates for route-specific absorbed doses is similar to that of Shehata (1985); for those compounds with greater permeability coefficients, the dermal absorption rate is a major factor in determining the contribution of a compound's dermal exposure to total absorbed dose relative to its exposure via other routes.

Jo et al. (1990a) performed studies to determine the chloroform doses to individuals during a 10-minute shower based on analyses of exhaled breath. Breath samples were collected, commencing at exactly 5 minutes after termination of showering, by using nonrebreathing two-way valves until a Tedlar sampling bag was filled with purified, humidified air being supplied through the valve from an inhalation bag. The pre-shower breath samples from all subjects were less than the detection limit of 0.83 $\mu g/m^3$. In one experiment, subjects showered normally with municipal water containing chloroform at 5.3 $\mu g/L$ to 36 $\mu g/L$, and the measured exhaled breath concentrations ranged from 6.0 $\mu g/m^3$ to 21.0 $\mu g/m^3$ (Least square mean (LSM) = 13 $\mu g/m^3$). In a companion experiment, subjects showered in the same shower stalls, but wore rubber clothes and boots to preclude dermal contact but to permit inhalation exposure. The water concentrations of chloroform ranged from 10 $\mu g/L$ to 37 $\mu g/L$, and the measured exhaled breath concentrations ranged from 2.4 $\mu g/m^3$ to 10 $\mu g/m^3$ (LSM = 6.8 $\mu g/m^3$). Jo et al. (1990a) reported that the LSM of the breath concentrations after normal showering (13 $\mu g/m^3$) represents the sum of inhalation and dermal exposures to chloroform during showering, while the LSM of the breath concentrations on those subjects wearing rubber suits (6.8 $\mu g/m^3$) represents inhalation exposure only. The increased exhaled air concentration after exposure to a normal shower (inhalation plus dermal) was statistically significant when compared to exposure from inhalation only, and Jo et al. (1990a) concluded that the difference, 6.2 $\mu g/m^3$, represents the dermal exposure. Thus, the dermal exposure as a fraction of inhalation exposure, was $6.2 \div 6.8 = 0.91176$ (= 92%). (Jo et al. [1990a]) reported the factor was 0.95, and Jo et al. [1990b] reported 0.93, but it would seem 0.92 is the correct factor.) Jo et al. [1990a,b] concluded that the mean internal dose to chloroform during showering was approximately equal for the dermal and inhalation exposure routes.

Jo et al. (1990b) compared the chloroform dose as estimated from showering with the water ingestion dose. For one shower per day, the inhalation exposure was 0.24 μg/kg-day and the dermal exposure was 0.22 μg/kg-day, for a total of 0.46 μg/kg-day. The chloroform ingestion doses were estimated based on daily water ingestion rates of either 0.15 L or 2L, and the "chloroform water concentration used was the value proportional to mean shower air concentration used for the inhalation dose calculation" (although the specific concentration used was not reported). Jo et al. (1990b) reported that the chloroform dose estimated for a daily 0.15-L water ingestion was 0.05 μg/kg-day and for a daily 2-L water ingestion was 0.7 μg/kg-day. Thus, the dermal and inhalation doses from one 10-minute shower per day were similar (0.22 and 0.24 μg/kg-day, respectively), and the doses from these routes are greater than the ingestion dose estimated from a 0.15-L water intake rate (0.05 μg/kg-day).

Where the same water supply is used for drinking and bathing, the importance of dermal contact with water can be evaluated by comparing the possible absorbed dose occurring during bathing relative to that occurring as a result of ingestion:

$$\frac{\text{Dermal Dose}}{\text{Ingestion Dose}} = \frac{2\ C_w\ K_P^w\ [6\ \tau\ t_{event}\ /\ \pi]^{0.5}\ A\ x\ EV}{C_w\ IR\ ABS_{GI}} \qquad (9.7)$$

where:

C_w = Contaminant concentration in water (mg/cm^3)
K_P^w = Permeability coefficient in water (cm/hour)
τ = Lag time (hr)

t_{event} = Exposure time (hr/event)
A = Exposed skin area (cm^2)
EV = Event/day (default assumption= 1 event/day)
IR = Water ingestion rate (L/day) x (1,000 cm^3/L)
ABS_{GI} = Fraction of contaminant absorbed in G.I. tract

Assuming an average adult ingestion rate (IR) of 2L/day, GI tract absorption fraction (ABS_{GI}) of 1, shower time of 10 minutes, and skin area of 20,000 cm^2, this ratio becomes:

$$\frac{Dermal\ Dose}{Ingested\ Dose} = 10\ K_p^w \sqrt{\tau} \tag{9.8}$$

So the dermal dose exceeds the ingested dose when:

$$K_p^w \sqrt{\tau} > 0.1 \tag{9.9}$$

The ratio of dermal dose to ingested dose for the above assumptions was computed for all compounds in Table 5-8 and plotted as a function of K_p's in Figure 9-2. This plot suggests that the dermal dose exceeds the ingested dose when the K_p is greater than about 0.1 cm/hour. It appears that most compounds of environmental concern have K_p's less than 0.1 (only about 20 of the 200 compounds in Table 5-8 have $K_p > 0.1$ cm/hour).

This analysis suggests that where the same water supply is used for drinking and bathing, dermal exposure while showering or bathing (for 10 minutes) is not important to consider for most contaminants, but may be important for the compounds which penetrate fastest. As the exposure time increases, the condition on K_p's will change accordingly, and more compounds with K_p's < 0.1 cm/hour will become of more concern.

Similar conclusions can be drawn for swimming. The discussion in Chapter 8 suggests default assumptions for time swimming implying a central estimate of about 3 hours/year to an upper estimate of 150 hours/year. Bathing time totals to 60 hours/year as the cumulative total of daily 10-minute baths. Thus, in situations where the same water source is used for swimming, bathing and drinking, the absorbed dose from dermal water contact may be 2 to 3 times as much as would occur from bathing alone, but would still be much less than direct ingestion for most contaminants.

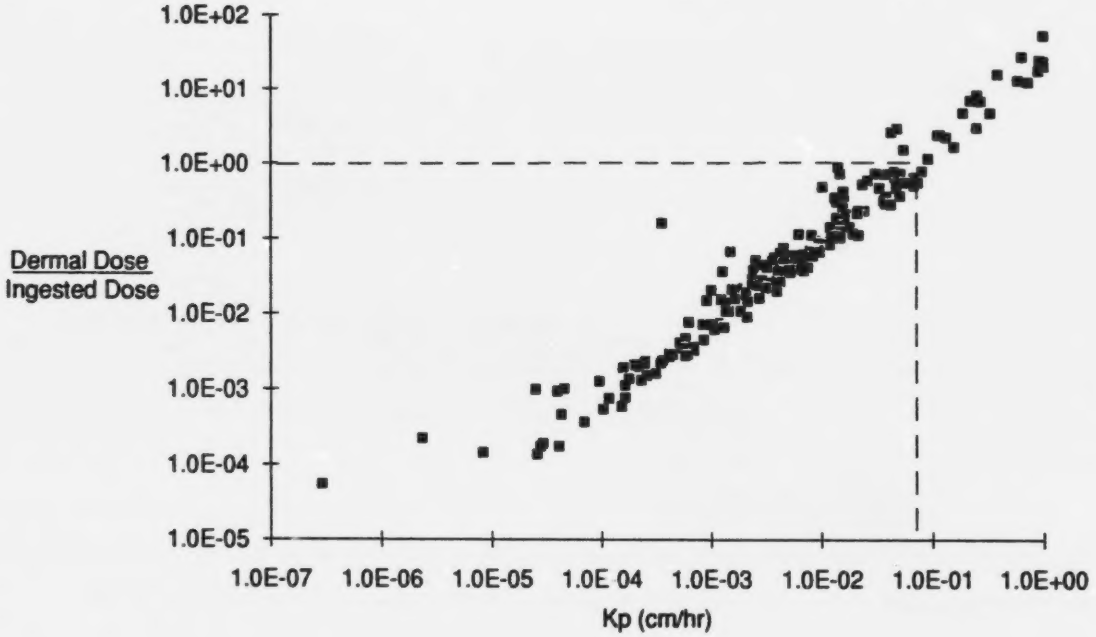

Figure 9-2. Ratio of dermal to ingested dose as a function of K_p.

Some experimental support for these conclusions can be found in the recent work by Jo et al. (1990a,b). Chloroform levels in breath after 10-minute showers were measured where the subjects first wore no clothing and then wore protective rubber suits. The breath levels dropped by about half when wearing the rubber suits, leading Jo et al. (1990a) to conclude that the chloroform dose from inhalation and dermal contact were about equal during normal showering. Jo et al. (1990b) also evaluated direct consumption of the water. The dose from ingestion of 2 L/day was estimated to be about 3 times greater than the dermal (or inhalation) dose alone. K_p values for chloroform have been measured to be in the range of 10^{-1} cm/hour. Thus, even a rapid permeant was found to cause a lower dose by dermal contact than by direct ingestion.

9.4. CONTRIBUTION OF DERMAL EXPOSURE TO THE TOTAL ABSORBED DOSE OF CHEMICAL VAPORS

In the studies outlined in Section 9.2., organic compounds that volatilized from drinking water were assumed to be absorbed by the respiratory tract. However, organic compounds in the vapor phase can also be absorbed across the skin, as discussed in Section 7.1.

Several investigators have estimated the contribution that dermal exposure to vapors would have to the total uptake of volatile organic compounds (VOCs). Blank and McAuliffe (1985) estimated that an adult with a skin surface area of 2 m^2 working in ambient air containing 10 ppm benzene and with 100 cm^2 of skin in contact with gasoline containing 5% benzene would absorb 7.5 μL of benzene from inhalation, 7.1 μL of benzene from dermal contact with liquid gasoline, and 1.5 μL from body exposure to ambient air in one hour. Blank and McAuliffe (1985) estimated the respiratory uptakes using a fraction absorbed for benzene in the respiratory tract of 0.46. This value was taken from Rusch et al. (1977), who reported that the average retention of inhaled benzene vapor was 46.3%. Dermal uptakes were estimated using a flux of 0.072 μl/cm^2-hour, which was measured in vitro using human skin. Therefore, based on these assumptions, of the total dose of benzene absorbed by this worker, approximately 9% will be contributed by dermal absorption of vapor-phase benzene.

Riihimaki and Pfaffli (1978) reported that sedentary volunteers exposed to 20 ppm xylene by inhalation for 3.5 hours absorbed a mean 357.2 μmole of the compound. Over a similar exposure period, subjects wearing respiratory protection, and exposed to 300 or 600 ppm xylene, absorbed 196.7 or 419.1 μmoles of xylene, respectively, via the dermal route. Although the exposure concentrations are different, the results of this study suggest that a worker, exposed to xylene at high concentrations and wearing only respiratory protection, could absorb a dose of xylene through the skin comparable to that absorbed via the respiratory tract at lower concentrations.

As discussed in Chapter 7, McDougal et al. (1987, 1990) obtained K_p values for chemical vapors in the rat. Using the following relationship, these researchers estimated the skin uptake of chemical vapors that could occur in rats if no respiratory protection was used:

$$\textit{Skin uptake ratio} = \frac{K_p A}{K_p A + Q_p} \tag{9.10}$$

where:

Q_p = Alveolar ventilation rate (cm^3/hour)
A = Surface area (cm^2)

Using this equation, the contribution of skin uptake in a mixed respiratory/dermal exposure scenario for a 210 g rat with a total surface area of 267 cm^2 and alveolar ventilation rate of 4.84 L/hour was calculated for a series of VOCs. These results are presented in Table 9-8.

Under these conditions, skin uptake of chemical vapors is expected to contribute about 9% of the total dose of styrene, and 3% to 4% of the total dose of m-xylene, toluene, and perchloroethylene. The findings of McDougal et al. (1990) that rat skin is generally 2 to 4 times more permeable to chemical vapors than human skin suggests that the contribution of chemical vapors to skin uptake in humans would be 2- to 4-fold less.

The studies of Blank and McAuliffe (1985), Riihimaki and Pfaffli (1978), and McDougal et al. (1987, 1990) suggest that dermal exposure to chemical vapors would contribute less than 10% of the total body burden of a VOC. In addition, Hursh et al. (1989) has described a scenario in which the dose of a volatile inorganic compound, mercury, taken up by the skin, is about 2.6% of the dose

Table 9-8. Contribution of Skin Uptake to the Total Absorbed Dose of Chemical Vapors in the Rat

Chemical	Concentration (ppm)	Flux (mg/cm^2/hour)	Permeability Constant (cm/hour)	Skin Uptake in a Mixed Exposure (%)
Styrene	3,000	0.0211	1.753 ± 0.105	9.4
m-Xylene	5,000	0.0151	0.723 ± 0.003	3.9
Toluene	8,000	0.0206	0.721 ± 0.007	3.7
Perchloroethylene	12,500	0.0541	0.668 ± 0.080	3.5
Benzene	40,000	0.0191	0.152 ± 0.006	0.8
Halothane	50,000	0.0180	0.045 ± 0.005	0.2
Hexane	60,000	0.0065	0.031 ± 0.004	0.1
Isoflurane	50,000	0.0096	0.025 ± 0.004	0.1

Source: McDougal et al. (1990)

that would be retained by the lung under the same conditions. Therefore, dermal exposure probably accounts for relatively little of the uptake of vapors of volatile organic or inorganic compounds.

Although the contribution of dermal exposure to the total absorbed dose of vapors may be minimal relative to other routes of exposure, the dose upon which risk estimations of VOCs are based may be underestimated by a factor of up to 10% for individuals with a substantial area of skin exposed to the contaminant. The results of these studies also suggest that workers wearing respiratory protection without chemical protective clothing may be at risk for absorbing a significant amount of the compound into the body, depending on the air concentration of the compound and the rate at which the vapors of the compound are absorbed through the skin.

9.5. CONTRIBUTION OF DERMAL EXPOSURE TO THE TOTAL ABSORBED DOSE OF COMPOUNDS IN THE SOIL

A comparison of the relative importance of different exposure pathways has also been performed for exposure to solvents in the soil. Using the approach developed by McKone (1989), Howd and co-workers presented a poster (Howd, R.A.; Schum, G.M.; McKone, T.E.; Wong, J.J. (1990) Risk estimation for solvents in soil. Poster presented at Society of Toxicology Meeting, Miami Beach, FL.) showing their estimates of dermal uptake of a number of VOCs from soil. Assuming 100% absorption via ingestion and inhalation of soil-bound VOCs, Howd et al. (1990) compared the relative uptake of several soil-adhered compounds from each route of exposure in three different exposure scenarios and made several conclusions regarding the importance of soil contact:

- Volatile solvents will generally be absorbed poorly from soils. However phenols and other compounds which are soluble in both water and lipids are an exception.
- Semivolatile or low volatility organics that are tightly adsorbed to soil (i.e., low water solubility) are poorly absorbed.
- Where direct exposure to soil occurs, generally the dermally absorbed dose will exceed the absorbed dose from ingestion or inhalation due to the greater amounts of soil contacted. However for very low volatility compounds like TCDD, ingestion is likely to be the major exposure route.

Where exposure to soil occurs by both dermal contact and soil ingestion, the importance of dermal contact can be evaluated by comparing it to ingestion. Soil ingestion occurring by hand-to-mouth or other activities (see discussion below) is likely to occur concurrently with dermal contact. Using typical parameter values for children, the exposures to soil can be estimated as follows:

$$Ingestion\ exposure = 200\ mg/day \qquad (9.11)$$

$$\begin{aligned} \textit{Dermal exposure} &= (\textit{contact rate})\ (\textit{total skin area})\ (\textit{fraction skin exposed}) \\ &= (0.2 \textit{ to } 1\ mg/cm^2\text{-}day)\ (10{,}000\ cm^2)\ (0.25) \\ &= 500 - 2{,}500\ mg/day \end{aligned} \tag{9.12}$$

These two scenarios suggest that a child may dermally contact 2 to 12 times more soil than he or she ingests. Accordingly, the absorbed dose would be greater by the dermal route if the gastrointestinal tract absorption fraction is less than 2 to 12 times greater than the dermal absorption fraction. Unfortunately, gastrointestinal tract absorption data are not readily available, and where available, they usually involve vehicles other than soil which may behave differently. Also, as discussed in Chapter 6, the data on dermal absorption from soils is still quite uncertain. Thus, this evaluation will generally be difficult to make with any degree of certainty. The gastrointestinal tract absorption of 2,3,7,8-TCDD in soil has been found to range from 20% to 40% (EPA, 1988a) and the dermal absorption fraction ranges from 1% to 10% (see Chapter 6). Using these factors in the scenario described above, the ingested dose could range from 40 to 80 mg/day and the dermal dose could range from 5 to 250 mg/day. This implies the dermal dose could be 16 times less to 6 times more than the ingested dose.

Key assumptions in this analysis are that the contact rate is a valid average for the entire exposed skin area and that the number of days of exposure by ingestion equal the number for exposure by contact. Also, the fraction of exposed skin used above (0.25) assumes the child is wearing shorts and short-sleeved shirt. In cold climates, this is probably not a valid assumption for much of the year.

The reasonableness of the suggestion that the amount of soil contacted would exceed the amount ingested is difficult to assess. Soil ingestion that occurs as a result of inadvertent hand-to-mouth activities is likely to be less than the amount contacted dermally since such activities would remove only a portion of the soil on hands and virtually none from other parts of the body. However, it is less obvious whether soil ingested during other types of activities would be less than soil contacting the skin. Activities other than inadvertent hand-to-mouth behavior which could cause soil ingestion include:

- Children may ingest soil via mouthing toys and other objects or surfaces.
- Soil may be ingested with normal foods.
- Soil particles suspended in the air can deposit in the mouth or respiratory tract and eventually be ingested.
- Abnormal or intentional soil ingestion behavior (i.e., pica) may result in high levels of ingestion.

In summary, much uncertainty surrounds the issue of how important dermal contact with soil is. For purposes of developing an interim screening level indicator of when dermal absorption should be considered, the following approach is recommended. Ignoring nonsteady-state issues and assuming that soil ingestion and dermal contact occur concurrently, that the best estimate default values for adults apply, and that 100% of the ingested dose is absorbed, the two routes can be compared as follows:

$$\begin{aligned} &\textit{dermal dose} = \textit{ingestion dose} \\ &C_{soil}\ ABS\ AF\ A\ EV = C_{soil}\ IR \\ &ABS = \frac{(100\ mg/day)}{[(0.2\ mg/cm^2\text{-}event)\ (1\ event/day)\ (5000\ cm^2)]} \\ &ABS = 0.1 \end{aligned} \tag{9.13}$$

Where:

C_{soil} = Contaminant concentration in soil (mg/mg)
ABS = Absorption fraction
AF = Soil to skin adherence rate (mg/cm^2-event)
A = Exposed skin surface area (cm^2)
EV = Event frequency (event/day) = 1 event/day (default assumption)
IR = Soil ingestion rate (mg/day)

On this basis, the general guideline can be offered that compounds with a dermal percent absorbed exceeding 10% are likely to be of greater potential concern than direct soil ingestion.

9.6. SUMMARY OF CONDITIONS THAT ENABLE DERMAL UPTAKE TO BECOME A SIGNIFICANT ROUTE OF EXPOSURE

From the results of the studies presented in this chapter, we can begin to identify the compound- and skin-specific factors that would result in dermal absorption becoming a major contributor to the total body burden of a compound.

Any factor that increases the rate or extent of dermal absorption of a compound and has no effect on the compound's pulmonary or oral uptake would be expected to increase the relative contribution of the dermal pathway to total dose. Two conditions that would be expected to increase dermal absorption relative to oral or respiratory uptake are damage to the stratum corneum and exposure of a large surface area of the exposed skin.

Prolonged exposure time might be expected to increase dermal and respiratory uptake equally. However, this factor would also be expected to increase the contribution of either of these routes to total absorbed dose, relative to the dose received by oral exposure. As shown by Brown et al. (1984) for a series of VOCs in drinking water, exposure time is a major factor in determining contribution of dermal uptake relative to ingestion.

As discussed in Chapter 2, a number of other factors affect the rate of dermal absorption. For example, increased temperature of the aqueous media may result in increased dermal absorption, but it may also increase the volatilization rate of VOCs from tap water, thereby making these compounds more available for respiratory uptake.

Chemical vapors are not expected to be significantly adsorbed by the skin; however, when adsorption and subsequent absorption does occur, it appears that the process is most affected by the lipid solubility of the compound. For soil-adsorbed compounds, the volatility of the compound and its capacity to bind to soil particles may be the major determinants of the relative contribution of dermal exposure to total absorbed dose.

From these factors, some general guidelines can be proposed to evaluate when the dose received from dermal contact with water, soil, and vapors is important to consider:

- For most contaminants, dermal contact with water during bathing or swimming will generally pose less threat than direct consumption of the water. The fastest penetrating contaminants may pose hazards similar to or greater than direct consumption. Although these chemicals may not increase the total risk substantially, they may significantly impact the cost of remedial action. This would occur in a situation where the water was considered unsafe to drink and the remedial action plan called for replacement of drinking water only, which could be accomplished via use of bottled water. Since it now appears that these chemicals would pose an equal risk via contact during bathing, it would be equally important to replace the water used for bathing and showering. For practical purposes, this suggests that replacing the entire household water supply would be necessary. It has not been well established how many of the environmental contaminants may have K_p values in this upper range, but it appears to be a minority.

- It appears that more soil is dermally contacted than is ingested during normal exposure scenarios. Dermal absorption from soils appears to be more significant than direct ingestion for those chemicals which have a percent absorbed exceeding about 10%.

- Current studies suggest that dermal exposure may be expected to contribute no more than 10% to the total body burden of those compounds present in the vapor phase. An exception may occur for workers wearing respiratory protection but not chemical protective clothing.

- Any compounds that are acutely toxic to the skin are important to consider even if less exposure occurs by skin contact than other routes.

10. STEPWISE DERMAL EXPOSURE ASSESSMENT PROCESS

This chapter describes the steps involved in quantifying the dermal absorption of contaminants from environmental media. The steps are derived from conclusions discussed in earlier chapters of this document. A review of these chapters will help the exposure/risk assessor in understanding the principles behind dermal exposure and better interpret the results of the process outlined here. Therefore, the exposure/risk assessor is encouraged to use this stepwise guidance in conjunction with the earlier supporting chapters.

The basic steps involved in a dermal exposure assessment are:

- Identification of contaminated environmental media;
- Identification of chemical contaminants and determination of their concentrations;
- Identification of activities resulting in dermal exposure and quantification of exposed skin area, contact rate (for soil related activities) and exposure time, frequency and duration;
- Identification and estimation of the number of dermally exposed individuals; and
- Selection, estimation, and evaluation of dermal absorption values.

Chapter 8 discusses each of the dermal exposure factors (event time, event frequency, duration, skin area, and soil adherence) and provides a range of default values to be used in situations where site-specific information is not available. As discussed in Chapter 8, the default values for the exposure factors were selected to represent a range of possible values from a central to an upper value. This chapter presents additional defaults for body weight and lifetime which are also needed to estimate dose. In accordance with Agency precedent, the defaults for body weight and lifetime are based on average values only (EPA, 1989a). No default value is provided for the medium concentration term in the dose equation since this is a purely site-specific value. As discussed in Chapter 8, selection of parameter values and their combination in the dose equation can create scenarios of varying severity. The Agency has not yet established procedures for how to create or define scenarios. However, a number of efforts are currently underway for this purpose, and it is hoped that standard procedures for creating scenarios will be defined soon that can be incorporated into future versions of this document. Meanwhile all that can be offered is the general guidance presented in Chapter 8. Basically, this is to select a combination of central and upper end values to create a high end scenario. See Chapter 8 for additional details.

This chapter presents guidance for aqueous and soil media separately, because they approach dermal absorption differently. The approach for estimating the dermal absorption of compounds in water is based on the use of a permeability coefficient, while the procedure for estimating the dermal absorption of soil-bound compounds is based on the use of an absorption fraction.

Although procedures for estimating dermal absorption of chemical vapors were discussed in Chapter 7 of this document, detailed steps for conducting such a dermal exposure assessment are not presented in this chapter. However, an example is included in Section 7.5. which outlines the assessment procedure. This decision was based on scope limits reflecting resource constraints and the priorities of the client office (see discussion in Chapter 1). Similarly, no specific guidance was offered on estimating the dermal absorption of compounds in sediment. Hopefully, future versions of this document can address both of these areas in more detail.

10.1. CONTACT WITH COMPOUNDS IN AQUEOUS MEDIA

This section presents the steps required to identify appropriate values for the exposure and absorption parameters, and how to combine these values to estimate the dermally absorbed dose of a compound in an aqueous medium.

Step 1. Select Values for Exposure Parameters

Site-specific measurement or modeling is required to identify values for the concentration of the contaminant(s) of interest in water. Concentration values should be used that are representative of the location and time period where exposure occurs. Lacking site-specific data to the contrary, the default values presented in Table 10-1 are recommended for the parameters characterizing water contact during bathing and swimming.

Table 10-1. Default Values for Water-Contact Exposure Parameters

Parameter	Bathing	Swimming
Adult Skin Area (cm^2)[a]	20,000 - 23,000	20,000 - 23,000
Event Time and Frequency	10 min/event, 1 event/day and 350 days/yr to 15 min/event, 1 event/day and 350 days/yr	0.5 hr/event, 1 event/day and 5 days/yr 1.0 hr/event, 1 event/day and 150 days/yr
Exposure Duration (years)	9 - 30	9 - 30

[a] Refer to Table 8-4 for age specific estimates of skin area.

Background information and the rationales supporting default recommendations are presented in Chapter 8 and briefly summarized here. The exposed skin area is based on the assumption that people are entirely immersed during bathing or swimming; the corresponding body areas were presented in Chapter 8. The bathing frequency of 350 days/year is based on information that most people bathe once per day (1 event/day). The bathing event time is based on the range (to be representative of baths as well as showers and considering that some water residue remains on skin for a brief period after bathing) given in the Exposure Factors Handbook (EPA, 1989a). The swimming event frequency and time is based on judgements regarding the behavior of someone who swims recreationally (central estimate) and someone who swims regularly for exercise (upper estimate). The exposure duration of 9 to 30 years represents the likely time that a person spends in one residence.

Step 2. Select Normalizing Parameters Used in Dose Equations

Dose estimates are normalized over body weight and time to express them in a manner that is consistent with dose-response relationships. An average body weight (70 kg for adults, see EPA, 1989a for age-specific values for children) is used for this purpose. For cancer risk assessments, an averaging time equal to a mean lifetime (70 yr) is used. For noncancer risk assessments, an averaging time equal to the exposure duration is used. (For more details regarding these parameters, see EPA, 1989a.)

Step 3. Estimate DA_{event}

Estimate DA_{event} using the procedures outlined in Section 5.3.

Step 4. Integrate Information to Determine Dermal Dose

Finally, the dermal dose is calculated by collecting the information from the earlier steps and substituting into the following equation.

$$DAD = \frac{DA_{event}\ EV\ ED\ EF\ A}{BW\ AT} \tag{10.1}$$

where:

DAD = Dermally Absorbed Dose (mg/kg-day)
DA_{event} = Absorbed dose per event (mg/cm^2-event)
A = Skin surface area available for contact (cm^2)
EV = Event frequency (events/day)
EF = Exposure frequency (days/year)
ED = Exposure duration (years)
BW = Body weight (kg)
AT = Averaging time (days), for noncarcinogenic effects AT = ED, and for carcinogenic effects AT = 70 year or 25,550 days

Step 5. Further Refinement of Dose Estimate

Where dose estimates are desired for children during specific age ranges, a summation approach is needed to reflect changes in skin surface area and body weight. Assuming all other exposure factors remain constant over time, Equation (10.1) is modified to:

$$DAD = \frac{DA_{event}\ EV\ EF}{AT} \sum_{i=m}^{n} \frac{A_i\ ED_i}{BW_i} \qquad (10.2)$$

where m and n represent the age range of interest. The skin surface areas for the ages of interest can be obtained from Table 8-4 and body weights from the Exposure Factors Handbook (EPA, 1989a).

Step 6. Evaluate Uncertainty

As explained in Chapter 5, the procedures for estimating the dermal dose from water contact are very new and must be approached with caution. One "reality check" that assessors should make for bathing scenarios is to compare the total amount of contaminant in the bathing water to the dose. The amount of contaminant in the water is easily computed by multiplying the contaminant concentration by the volume of water used (showers typically use 5 to 15 gal/min). Obviously, the dose cannot exceed the amount of contaminant in the water. In fact, it seems unlikely that a high percentage of the contaminant in the water could be dermally absorbed. As a preliminary guide, if the dermal dose estimate exceeds 50% of the contaminant in the water, the assessor should question the validity of the dose estimate. Volatile compounds have been shown to volatilize significantly during showering. Andelman (1988) found that about 90% of TCE volatilized during showering. This would suggest that the effective concentration of the contaminant in water and resulting dermal dose may be reduced. So for volatile compounds, assessors may want to assume a reduced contaminant concentration in water contacting the skin.

The dermal permeability estimates are probably the most uncertain of the parameters in the dermal dose equation. As discussed in Chapter 5, the measured values probably have an uncertainty of plus or minus a half order of magnitude. Accordingly, the final dose and risk estimates must be considered highly uncertain. Some idea of the range of possible values can be obtained by first using average or typical values for each parameter to get a typical dose estimate. Second, by setting two or three of the most variable parameters to their upper values and the others to their average values to get some idea of the possible upper-dose estimate.

10.2. CONTACT WITH COMPOUNDS IN SOIL

This section presents the steps required to identify appropriate values for the exposure and absorption parameters, and how to combine these values to estimate the dermally absorbed dose of a compound in soil.

Step 1. Select Values for Exposure Parameters

Site-specific measurement or modeling is required to identify values for the concentration of the contaminant(s) of interest in soil. Concentration values should be used that are representative of the location and time period where exposure occurs. Lacking site-specific data to the contrary, the default values presented in Table 10-2 are recommended for the parameters characterizing soil contact.

Table 10-2. Default Values for Soil

Parameter	Default Value
Adult Skin Area Available for Contact[a] (cm^2)	5,000 - 5800
Soil to Skin Adherence Rate (mg/cm^2-event)	0.2 - 1.0
Exposure Frequency (events/year)	40 - 350
Exposure Duration (years)	9 - 30

[a] Refer to Table 8-4 for age-specific estimates of the skin area.

Background information and the rationales supporting default recommendations are presented in Chapter 8 and briefly summarized here. The adherence rate values were derived from the measured adherence values presented in Chapter 8. The exposed skin area is based on the assumption that 25% of the body is exposed which corresponds roughly to wearing shoes, shorts, and short sleeved shirts; the corresponding body areas were presented in Chapter 8. The event frequency of 40 to 350 events/year is based on judgements regarding behavior involving soil contact such as gardening. The exposure duration of 9 to 30 years represents the time that a person spends in one residence (EPA, 1989a).

Step 2. Select Normalizing Parameters Used in Dose Equation

Dose estimates are normalized over body weight and time to express them in a manner that is consistent with dose-response relationships. An average body weight (70 kg for adults, see EPA, 1989a for age-specific values) is used for this purpose. For cancer risk assessments, an averaging time equal to a mean lifetime (70 yr) is used. For noncancer risk assessments, an averaging time equal to the exposure duration is used. (For more details regarding these parameters, see EPA, 1989a.)

Step 3. Estimate DA_{event}

Estimate DA_{event} using the procedures outlined in Section 6.4.

Step 4. Integrate Information to Determine Dermal Dose

Finally, the dermal dose is calculated by collecting information from the earlier steps and substituting into the following equation.

$$DAD = \frac{DA_{event}\ EF\ ED\ A}{BW\ AT} \tag{10.3}$$

where:

DAD = Dermally Absorbed Dose (mg/kg-day)

DA_{event} = Absorbed dose per event (mg/cm^2-event)
A = Skin surface area available for contact (cm^2)
EF = Exposure frequency (events/year)
ED = Exposure duration (years)
BW = Body weight (kg)
AT = Averaging time (days), for noncarcinogenic effects AT = ED, and for carcinogenic effects AT = 70 year or 25,550 days

Step 5. Further Refinement of Dose Estimate

Where dose estimates are desired for children during specific age ranges, a summation approach is needed to reflect changes in skin surface area and body weight. Assuming all other exposure factors remain constant over time, Equation (10.3) is modified to:

$$DAD = \frac{DA_{event}\ EF}{AT} \sum_{i=m}^{n} \frac{A_i\ ED_i}{BW_i} \tag{10.4}$$

where m and n represent the age range of interest. The skin surface areas for the ages of interest can be obtained from Table 8-4 and body weights from the Exposure Factors Handbook (EPA, 1989a).

Step 6. Evaluate Uncertainty

Some idea of the uncertainty can be obtained from the range of percent absorbed values reported in Chapter 6. However, these ranges reflect differences among a very limited set of experiments and do not vary much in some cases. Additionally, the amount of soil adhering to skin and exposure frequency/duration are highly uncertain. Accordingly, final dose and risk estimates must be considered highly uncertain. First, some idea of the range of possible values can be obtained by using average or typical values for each parameter (use the center of the percent absorbed range where available) to get a typical dose estimate. Second, by setting two or three of the most variable parameters to their upper values and the others to their average values to get some idea of the possible upper-dose estimate.

10.3. USE OF DERMAL ABSORPTION DATA IN RISK ASSESSMENT

The procedures outlined in this document allow the exposure/risk assessor to derive an estimate of dermally absorbed dose. This absorbed dose information is best suited for evaluating the risk of chronic systemic health effects. As mentioned in the Introduction to this document, assessment of acute and or point-of-entry effects is outside the primary focus of this document. However, brief discussions on point-of-entry effects are presented in Sections 7.4. and 9.1.

The procedures for estimating chronic systemic health effect risks from dose estimates are as follows:

$$Cancer\ Risk = 1 - \exp\left(-DAD \times q^{*}\right) \tag{10.5}$$

$$Hazard\ Index\ for\ Non\text{-}Cancer\ Effects = \frac{DAD}{RfD} \tag{10.6}$$

where,

DAD = Dermally absorbed dose (mg/kg-day)
q* = 95% upper-confidence limit of the linear-slope factor (kg-day/mg)
RfD = Reference Dose (mg/kg-day)

The latest information on RfD's and slope factors can be obtained from EPA's Integrated Risk Information System or IRIS (EPA, 1990b). Unfortunately, all of the slope factors and RfD's in IRIS are based on ingestion or inhalation rather than dermal contact. Until more appropriate dose-response factors are available, it is recommended that assessors use the oral factors (although as discussed in Section 7.4. the inhalation factors may be useful for assessing skin effects due to vapor contact). It is important that assessors emphasize the uncertainty in this approach. These factors were derived from oral studies and intended for assessing risks from ingestion. Obviously, the response of a living system to an oral dose may differ significantly from the response to a dermal dose. The most obvious difference is that the risk associated with point-of-entry (skin) effects for locally acting toxic agents cannot be estimated from oral toxicity data. Furthermore, unlike orally administered compounds, dermally applied chemicals would not be subjected to first-pass hepatic metabolism before reaching the systemic circulation. Therefore, a toxic effect attributable to an active metabolite might be more pronounced if the compound was administered orally. Conversely, the dermal absorption of a toxic parent compound that undergoes little or no first-pass metabolism may result in a greater dose of the toxic moiety entering the systemic circulation than if the compound was absorbed orally. Thus, the application of these oral dose-response relationships to dermal doses introduces considerable uncertainty.

In addition to the uncertainties caused by route differences, further uncertainty is introduced by the fact that the oral dose-response relationships are based on potential (i.e., administered) dose, whereas the dermal dose estimates are absorbed doses. Ideally, these differences in route and dose type should be resolved via pharmacokinetic modeling. Alternatively, if estimates of the gastrointestinal absorption fraction are available for the compound of interest in the appropriate vehicle, then the oral dose-response factor, unadjusted for absorption, can be converted to an absorbed dose basis as follows (see related discussion in Appendix A of RAGS, EPA, 1989b):

$$\begin{aligned} RfD_{absorbed} &= RfD_{administered} \times ABS_{GI} \\ q^{*}_{absorbed} &= q^{*}_{administered} \,/\, ABS_{GI} \end{aligned} \tag{10.7}$$

Lacking this information, the oral factor should be used as is accompanied by a strong statement emphasizing the uncertainty involved.

GLOSSARY

Absorption: The process by which a substance is transported across the skin permeability surface barrier and taken up into the living tissue of the body; generally synonymous with percutaneous absorption and with dermal uptake.

Absorbed Dose: The amount of a substance penetrating across an absorption barrier (the exchange boundaries) of an organism, via either physical or biological processes. Sometimes called internal dose.

Absorption Barrier: Any of the exchange barriers of the body that allow differential diffusion of various substances across a boundary. Examples of absorption barriers are the skin, lung tissue, and gastrointestinal tract wall.

Absorption Fraction: The relative amount of a substance on the skin that penetrates through the epidermis into the body; reported as the unitless fraction of the applied dose or as the percent absorbed.

Administered dose: The amount of a substance given to a test animal in determining dose-response relationships, esp. through ingestion or inhalation. In exposure assessment, since exposure to chemicals is usually inadvertent, this quantity is called applied dose.

Adsorption: Adherence of a solid or liquid to a surface without penetrating through the surface layer. Also, the adherence of ions or organic chemicals onto the surface layer of other materials without being incorporated into or absorbed by the surface of the material.

Agent: A chemical, radiological, mineralogical, or biological entity that may cause deleterious effects in an organism after the organism is exposed to it.

Ambient: Surrounding conditions.

Ambient Medium: One of the basic categories of material surrounding or contacting an organism, e.g., outdoor air, indoor air, water, or soil, through which chemicals or pollutants can move and reach the organism. (See biological medium, environmental medium)

Applied Dose: The amount of a substance in contact with the primary absorption boundaries of an organism (e.g., skin, lung, gastrointestinal tract) and available for absorption.

Aqueous: Relating to water or substances dissolved or suspended in water; not to be confused with other liquid solutions or suspensions not containing water.

Bioavailability: The state of being capable of being absorbed and available to interact with the metabolic processes of an organism. Bioavailability is typically a function of chemical properties, physical state of the material to which an organism is exposed, and the ability of the individual organism to physiologically take up the chemical.

Biological Measurement: A measurement taken in a biological medium. For the purpose of exposure assessment via reconstruction of dose, the measurement is usually of the concentration of a chemical/metabolite or the status of a biomarker, normally with the intent of relating the measured value to the internal dose of a chemical at some time in the past. (Biological measurements are also taken for purposes of monitoring health status and predicting effects of exposure.) (See ambient measurement)

Biological Medium: One of the major categories of material within an organism, e.g., blood, adipose tissue, or breath, through which chemicals can move, be stored, or be biologically, physically, or chemically transformed. (See ambient medium, environmental medium)

Biologic Marker of Exposure (sometimes referred to as a biomarker of exposure): Exogenous chemicals, their metabolites, or products of interactions between a xenobiotic chemical and some target molecule or cell that is measured in a compartment within an organism.

Body Burden: The amount of a particular chemical stored in the body at a particular time, especially a potentially toxic chemical in the body as a result of exposure. Body burdens can be the result of long term or short term storage, for example, the amount of a metal in bone, the amount of a lipophilic substance such as PCB in adipose tissue, or the amount of carbon monoxide (as carboxyhemoglobin) in the blood.

Cutaneous: Of, relating to, or affecting the skin.

Dermal Adherence Capacity: The maximum amount of a specified matrix that can be contained on the skin.

Dermal Adsorption: The process by which materials come in contact with the skin surface, but are then retained and adhered to the permeability barrier without being taken into the body.

Dermally Absorbed Dose: The amount of the applied material (the dose) which becomes absorbed into the body.

Dermal Exposure: Contact with the skin by any medium containing chemicals, quantified as the amount on the skin and available for adsorption and possible absorption.

Dermis: The highly vascularized inner mesodermic layer of the skin, about 500 to 3,000 μm thick, which is a collagenous, hydrous layer and contains the outermost nerve endings of the skin.

Diffusion Cell: For in vitro skin penetration testing, any system of chambers for holding test materials, between the two compartments of which a section of skin or its membrane components is stretched to assess the transport of a chemical or chemicals from the donor side to the receptor side to measure the flux of the chemical(s) across the skin or its membrane components.

Donor: In a diffusion cell, that material (neat or test compound in a vehicle) placed on the skin or its membrane components, from which the loss of the test compound is measured over time to develop an estimated flux value.

Dose: The amount of a substance available for interaction with metabolic processes after crossing the outer boundary of an organism. The applied dose is the amount of a substance presented to an absorption barrier and available for absorption (although not necessarily having yet crossed the outer boundary of the organism). The internal dose is the amount crossing an absorption barrier (e.g., the exchange boundaries of skin, lung, and digestive tract) through uptake processes. The amount of the chemical available for interaction by any particular organ or cell is termed the delivered dose for that organ or cell.

Dose Rate: Dose per unit time, for example in mg/day, sometimes also called dosage. Dose rates are often expressed on a per-unit-body-weight basis, yielding units such as mg/kg/day (mg/kg • day). They are also often expressed as averages over some time period, for example a lifetime.

Dose-Response Assessment: The determination of the relationship between the magnitude of administered, applied, or internal dose and the probability of occurrence of the health effects in question.

Dose-Response Curve: A quantitative relationship between administered, applied, or internal dose and probability of occurrence of a health effect or effects. Results are usually expressed in units of incidence per unit dose.

Dosimeter: Instrument to measure dose; many so-called dosimeters actually measure exposure rather than dose.

Dosimetry: Process of measuring dose.

Electrolyte: A substance that will provide ionic conductivity when dissolved in water or when in contact with it; such compounds may be either solid or liquid. A substance that will ionize in solution and increase the conductivity of the aqueous medium.

Environmental Fate: The destiny of a chemical or biological pollutant after release into the environment. Environmental fate involves temporal and spatial considerations of transport, transfer, storage, and transformation.

Environmental Fate Model: In the context of exposure assessment, any mathematical abstraction of a physical system used to predict the concentration of specific chemicals as a function of space and time subject to transport, intermedia transfer, storage, and degradation in the environment.

Environmental Medium: One of the major categories of material found in the outdoor natural physical environment that surrounds or contacts organisms, e.g., surface water, ground water, soil, or air, and through which chemicals or pollutants can move and reach the organisms. (See ambient medium, biological medium)

Environmental Pollutant: Any entity which contaminates any ambient media, including surface water, groundwater, soil, or air.

Epidermis: The outer mesodermic layer of the skin; a non-vascular layer about 100 μm thick, with the outermost layer, the stratum corneum of about 10 to 40 μm thickness composed of dead, partially desiccated and keratinized epidermal cells; below the stratum corneum lies the stratum germinativum, or viable epidermis, a layer about 50 to 100 μm thick composed of rapidly proliferating nucleated cells, generating about one new cell layer per day, resulting in the stratum corneum becoming totally replaced once every 2 to 3 weeks.

Exposure: Contact of a chemical, physical, or biological agent with the outer boundary of an organism. Exposure is quantified as the concentration of the agent in the medium in contact integrated over the time duration of that contact.

Exposure Assessment: The determination or estimation (qualitative or quantitative) of the magnitude, frequency, duration, and route of exposure.

Exposure Pathway: The course a chemical or pollutant takes from the source to the organism exposed.

Exposure Route: The way a chemical or pollutant enters an organism after contact, e.g., by ingestion, inhalation, or dermal absorption.

Exposure Scenario: A set of facts, assumptions, and inferences about how exposure takes place that aids the exposure assessor in evaluating, estimating, or quantifying exposures.

Fat/Air Partition Coefficient: The relationship between lipid solubility (and thus permeability into skin) and vapor phase transport (and thus relative volatilization rate and vapor pressure) for organic compounds. A compound with a high fat/air partition coefficient would have a high lipid solubility and/or low potential to enter into the vapor phase, while a compound with a low fat/air partition coefficient would have a low lipid solubility and/or a high potential to volatilize and remain in the vapor phase. Compare with octanol/water partition coefficient.

Fick's First Law of Diffusion: As applied to skin, the transdermal flux of a compound is proportional to the concentration gradient of the compound (ΔC) across the dermal barrier, represented by $J = K_p \times \Delta C$.

Fixed Location Monitoring: Sampling of an environmental or ambient medium for pollutant concentration at one location continuously or repeatedly over some length of time.

Flux: Amount of chemical absorbed across a defined surface area of the skin per unit time ($mg/cm^2/hr$). This is equal to the dermal permeability coefficient multiplied by the concentration of the chemical. Flux and concentration are interdependent.

Geometric Mean: The nth root of the product of n values.

Hazard Identification: The determination of whether a particular substance or chemical is or is not causally linked to particular health effects.

Hydrophilic: Literally "water loving"; the property of a chemical to have a strong tendency to bind or absorb water.

Hydrophobic: Literally "water hating"; the property of a chemical to be antagonistic to water or incapable of dissolving in water (and for many organic chemicals, to be soluble in fats and oils, or non-polar solvents).

Infinite Dose: A procedure used during in vitro testing to help ensure that steady state conditions are maintained. Basically, it involves using a sufficiently high concentration of permeant in the donor solution such that it remains constant over the course of the experiment.

Intake: the process by which a substance crosses the outer boundary of an organism without passing an absorption barrier, e.g., through ingestion or inhalation.

Internal Dose: The amount of a substance penetrating across an absorption barrier (the exchange boundaries) of an organism, via either physical or biological processes. Sometimes called absorbed dose.

In Vitro: Literally "in glass"; a situation in which an experiment is carried out in a vessel (glass container, test tube, beaker, or diffusion cell) using excised tissues.

In Vivo: Literally "in life"; a situation in which an experiment is carried out using living, intact organisms.

Lipophilic: Literally "lipid loving"; the property of a chemical to have a strong affinity for lipids, fats, or oils; or being highly soluble in nonpolar organic solvents.

Lipophobic: Literally "lipid hating"; the property of a chemical to be antagonistic to lipids or incapable of dissolving in or dispersing uniformly in fats, oils, or nonpolar organic solvents.

Matrix: The material or medium in which something is enclosed, embedded, dispersed or dissolved.

Maximally Exposed Individual (MEI): The single individual with the highest exposure in a given population.

Median Value: The value in a measurement data set such that half the measured values are greater and half are less.

Medium (pl. media): Any one of the basic categories of material surrounding or contacting an organism (e.g., outdoor air, indoor air, water, soil, sediments) through which chemicals or pollutants can move and reach the organism.

Microenvironment Method: A method used in predictive exposure assessments to estimate exposures by sequentially assessing exposure for a series of areas (microenvironments) that can be approximated by constant or well characterized concentrations of a chemical or other agent.

Microenvironments: Well-defined areas such as the home, office, automobile, kitchen, store, etc. that can be treated as homogeneous (or well characterized) in the concentrations of a chemical or other agent.

Mode: The value in the data set that occurs most frequently.

Monte Carlo Technique: a repeated random sampling from the distribution of values for each of the parameters in a generic (exposure or dose) equation to derive an estimate of the distribution of (exposures or doses in) the population.

Neat: Pure material, undiluted, free from admixture.

Non-parametric Statistical Methods: Methods that do not assume a particular statistical distribution for the statistical population(s) of interest ("distribution-free methods").

Partition Coefficient: The vehicle-specific relationship of a chemical and its relative presence within two competing media (such as between water and n-octanol in the octanol/water partition coefficient); expressed as the ratio of the amounts in each medium at steady state.

Pathway: The course a chemical or pollutant takes from the source to the organism exposed. Personal measurement - A measurement collected from an individual's immediate environment using active or passive devices to collect the samples.

Percutaneous: Performed or effected through the skin.

Permeability Coefficient: A flux value, normalized for concentration, that represents the rate at which a chemical penetrates the skin (cm/hr).

Permeable: Penetrable; capable of permitting materials (liquids, gases, dissolved chemicals) to pass through (a permeable membrane).

Pharmacokinetics: The study of the time course of absorption, distribution, metabolism, and excretion of a foreign substance (e.g., a drug or pollutant) in an organism's body.

Physiologically-Based Pharmacokinetic Modeling (PBPK): For dermal exposure testing, use of models to estimate the dermal permeability constant and amounts absorbed by the best-fit method based on blood concentration-time profile data or by monitoring the appearance and amounts of metabolites in post-exposure urine samples or by measuring the concentration of parent compound in the expired air.

Point-of-contact Measurement of Exposure: An approach to quantifying exposure by taking measurements of concentration over time at or near the point of contact between the chemical and an organism while the exposure is taking place.

Polarity: The quality or condition inherent in something (a body, electric cell, membrane, chemical, etc.) that exhibits opposing properties or powers in opposite parts or directions; a polar molecule has positive and negative electrical charges which are permanently separated, and polar molecules ionize in solution and impart electrical conductivity; polar membranes have opposite (or differing) charges on the inside and outside of the membranes.

Potential Dose: The amount of a chemical contained in material ingested, air breathed, or bulk material applied to the skin.

Receptor Fluid: In a diffusion cell, the liquid in the compartment opposite the donor cell, and which started with none or very little of the test material and receives the material transporting across the whole skin or epidermis, to permit measurements of the flux of the material. (see **Donor**)

Reconstruction of Dose: An approach to quantifying exposure from internal dose, which is in turn reconstructed after exposure has occurred, from evidence within an organism such as chemical levels in tissues or fluids, or from evidence of other biomarkers of exposure.

Risk: The probability of deleterious health or environmental effects.

Risk Characterization: The description of the nature and often the magnitude of human or non-human risk, including attendant uncertainty.

Route: The way a chemical or pollutant enters an organism after contact, e.g., by ingestion, inhalation, or dermal absorption.

Scenario Evaluation: An approach to quantifying exposure by measurement or estimation of both the amount of a substance contacted, and the frequency/duration of contact, and subsequently linking these together to estimate exposure or dose.

Skin Adherence: The property of a material which causes it to be retained on the surface of the epidermis (adheres to the skin).

Source Characterization Measurements: Measurements made to characterize the rate of release of agents into the environment from a source of emission such as an incinerator, landfill, industrial or municipal facility, consumer product, etc.

Steady State: The status or condition of a system or process that has reached an equilibrium over time and then does not change, or a condition that changes only negligibly over a specified time.

Stratum Corneum: The outermost layer of the skin (see **Epidermis**) composed of dead, partially desiccated and keratinized epidermal cells; thought to provide the major resistance to the absorption into the circulation of substances that are deposited on the skin.

Surrogate Data: Substitute data or measurements on one substance used to estimate analogous or corresponding values of another substance.

Uptake: The process by which a substance crosses an absorption barrier and is absorbed into the body.

REFERENCES

Ackermann, C.; Flynn, G. (1987) Ether-water partitioning and permeability through nude mouse skin in vitro. I. Urea, thiourea, glycerol and glucose. Intl. J. Pharmacol. 36:61-66.

Agren, M.S. (1990) Percutaneous absorption of zinc from zinc oxide applied topically to intact skin in man. Dermatologica 180(1):36-39.

Albery, W.J.; Hadgraft, J. (1979) Percutaneous absorption: theoretical description. J. Pharm. Pharmacol. 31:140-147.

American Conference of Governmental Industrial Hygienists (ACGIH). (1990-1991) Theshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH.

Andelman, J. B. (1988) Total exposure to volatile organic compounds in potable water. In: Ram, N.; Christman, R.; Cantor, K., eds. Significance and treatment of volatile organic compounds in water supplies. Chelsea, MI: Lewis Publishers, Inc.

Andersen, B.D.; Higuchi, W.I.; Raykar, P.V. (1988) Heterogeneity effects on permeability - partition coefficient relationships in human stratum corneum. Pharm. Res. 5(9):566-573.

Atherton, D.J.; Rook, A. (1986) The newborn. In: Rook, A.; Wilkinson, D.S.; Ebling, F.J.; Champion, R.H.; Burton, J.L., eds. Textbook of dermatology. 4th ed. New York, NY: Blackwell Scientific Press; pp. 229.

Banks, Y.B.; Birnbaum, L. (1991) Dermal absorption of TCDD: effect of age. In: Knaak J.A.B.; Mailbach H.I. eds. Health risk assessment through dermal and inhalation exposure and absorption of toxicants. Boca Raton, FL: CRC Press Inc.

Banks, Y.B.; Brewster, D.W.; Birnbaum, L.S. (1989) Age-related changes in dermal absorption of TCDD and 2,3,4,7,8-pentachlorodibenzofuran (4PeCDF). Toxicology 9:118.

Baranowska-Dutkiewicz, B. (1968) Investigations on the absorption of carbon disulphide through the human skin. II. Absorption of liquid CS_2 and its aqueous solutions (In Polish). Zes. Nauk. Bromat. Chem. Tosykol., 1:159.

Baranowska-Dutkiewicz, B. (1981) Absorption of hexavalent chromium by skin in man. Arch. Toxicol. 47:47-50.

Baranowska-Dutkiewicz, B. (1982) Skin absorption of aniline from aqueous solutions in man. Toxicol. Lett. 10:367-372.

Barker, N.; Hadgraft, J.; Rutter, N. (1987) Skin permeability in the newborn. J. Invest. Dermatol. 88(4):409-411.

Barnes, D.G.; Dourson, M.D. (1989) Reference Dose (RfD): description and use in health risk assessments. Regul. Toxicol. Pharmacol. 8:471-486.

Barrow, C.S. (1989) Generation and characterization of gases and vapors. In: McClellan, R.O.; Henderson, R.F., eds. Concepts in inhalation toxicology. New York, NY: Hemisphere Publishing Corp; pp. 63-84.

Barry, B.W.; Harrison, S.M.; Dugard, P.H. (1985) Vapor and liquid diffusion of model penetrants through human skin: correlation with thermodynamic activity. J. Pharm. Pharmacol. 37:226-236.

Behl, C.R.; Flynn, G.L.; Kurihara, T.; Harper, N.; Smith, W.; Higuchi, W.I.; Ho, N.F.H.; Pierson C.L. (1980) Hydration and percutaneous absorption. I. Influence of hydration on alkanol permeation through hairless mouse skin. J. Invest. Dermatol. 75:346-352.

Behl, C.R.; El-Sayed, A.A.; Flynn, G.L. (1983a) Hydration and percutaneous absorption. IV. Influence of hydration on *n*-alkanol permeation through rat skin, comparison with hairless and Swiss mice. J. Pharm. Sci. 72:79-82.

Behl, C.R.; Linn, E.E.; Flynn, G.L.; Pierson, C.L.; Higuchi, W.I.; Ho, N.F.H. (1983b) Permeation of skin and eschar by antiseptics. I. Baseline studies with phenol. J. Pharm. Sci. 72(4):391-396.

Behl, C.R.; Flynn, G.L.; Kurihara, T.; Smith, W.M.; Bellantone, N.H.; Gatmaitan, O.; Higuchi, W.I.; Ho, N.F.H. (1984) Age and anatomical site influences on alkanol permeation of skin of the male hairless mouse. J. Soc. Cosmet. Chem. 35:237-252.

Bentley, P.; Schuassmann, H.; Sims, P.; Oesch, F. (1976) Epoxides derived from various polycyclic hydrocarbons as substrates of homogenous and microsome bound epoxide hydratase. Eur. J. Biochem. 69:97-103.

Berliner, D.; Pasqualini, J.; Gallegos, A. (1968) The formation of water soluble steroids by human skin. J. Invest. Dermatol. 50:220-224.

Berner, B.; Cooper, E.R. (1987) Models of skin permeability. In: Berner, B.; Keygondus, A.S., eds. Transdermal delivery of drugs, v. 3. Boca Raton, FL: CRC Press; pp. 41-56.

Blank, I.H. (1964) Penetration of low molecular weight alcohols into skin. I. The effect of concentration of alcohol and type of vehicle. J. Invest. Dermatol. 43:415.

Blank, I.H.; McAuliffe, D.J. (1985) Penetration of benzene through human skin. J. Invest. Dermatol. 85:522-526.

Blank, I.H.; Scheuplein, R.J. (1969) Transport into and within the skin. Br. J. Dermatol. 81(Suppl.):4-10.

Blank, I.H.; Scheuplein, R.J.; MacFarlane, D.J. (1967) Mechanism of percutaneous absorption. III. The effect of temperature on the transport of non-electrolytes across the skin. J. Invest. Dermatol. 49(6):582-589.

Bogen, K.T.; Colston, B.W.; Machicao, L.K. (1992) Dermal absorption of dilute aqueous chloroform, trichloroethylene, and tetrachloroethylene in hairless guinea pigs. Fundam. Appl. Toxicol. 18:30-39.

Bond, J.; Barry, B. (1988) Limitations of hairless mouse for in vitro permeation studies through human skin: hydration damage. J. Invest. Dermatol. 90:486-489.

Boyd, E. (1935) The growth of the surface area of the human body. Minneapolis, MN: University of Minnesota Press.

Brewster, D.W.; Bank, Y.B.; Clark, A.M.; Birnbaum, L.S. (1989) Comparative dermal absorption of 2,3,7,8-tetrachlorodibenzo-p-dioxin and three polychlorinated dibenzofurans. Toxicol. Appl. Pharmacol. 97:156-166.

Bronaugh, R.L. (1982) Percutaneous absorption of cosmetic ingredients. In: Frost, P. Principles of cosmetics for the dermatologist. St. Louis, MO: C.V. Mosby; pp. 277-284.

Bronaugh, R.L.; Barton, C.N. (1991) Prediction of human percutaneous absorption with physicochemical data. In: Wang, R.G.; Maibach, H.I. eds. Health risk assessment through dermal and inhalation exposure and absorption of toxicants. Boca Raton, FL: CRC Press. Submitted.

Bronaugh, R.L.; Congdon, E.R. (1984) Percutaneous absorption of hair dyes: correlation with partition coefficients. J. Invest. Dermatol. 83:124-127.

Bronaugh, R.L.; Maibach, H.I. (1983) In vitro percutaneous absorption. In: Marzulli, F.N.; Maibach, H.I. eds., Dermatotoxicology. Washington, DC: Hemisphere Press; pp 117-129.

Bronaugh, R.L.; Maibach, H.I. (1985) Percutaneous penetration of nitroaromatic compounds. J. Invest. Dermatol. 84:180-183.

Bronaugh, R.L.; Stewart, R.F. (1984) Methods for in vitro percutaneous absorption studies. III. Hydrophobic compounds. J. Pharm. Sci. 73:1255.

Bronaugh, R.L.; Stewart, R.F. (1985) Methods for in vitro percutaneous absorption studies. V. Permeation through damaged skin. J. Pharm. Sci. 74(10):1062-1066.

Bronaugh, R.L.; Stewart, R.F. (1986) Methods for in vitro percutaneous absorption studies. VI. Preparation of the barrier layer. Am. Pharm. 75(5):487-491.

Bronaugh, R.L.; Congdon, E.R.; Scheuplein, R.J. (1981) The effect of cosmetic vehicles on the penetration of N-nitrosodiethanolamine through excised human skin. J. Invest. Dermatol. 76(2):94-96.

Bronaugh, R.L.; Stewart, R.F.; Congdon, E.R.; Giles, A.L. (1982a) Methods for in vitro percutaneous absorption studies. I. Comparison with in vivo results. Toxicol. Appl. Pharmacol. 62:474-480. Submitted.

Bronaugh, R.L.; Stewart, R.F.; Congdon, E.R. (1982b) Methods for in vitro percutaneous absorption studies. II. Animal models for human skin. Toxicol. Appl. Pharmacol. 62:481-488.

Bronaugh, R.L.; Stewart, R.F.; Congdon, E.R. (1983) Differences in permeability of rat skin related to sex and body site. J. Soc. Cosmet. Chem. 34:127-135.

Bronaugh, R.L.; Stewart, R.F.; Wester, R.C.; Bucks, D.; Maibach, H.I.; Anderson, J. (1985) Comparison of percutaneous absorption of fragrances by humans and monkeys. Food Chem. Toxicol. 23(1):111-114.

Bronaugh, R.L.; Weingarten, D.P.; Lowe, N.J. (1986a) Differential rates of percutaneous absorption through the eczematous and normal skin of a monkey. J. Invest. Dermatol. 87(4):451-453.

Bronaugh, R.L.; Stewart, R.F.; Simon, M. (1986b) Methods for in vitro percutaneous absorption studies. VII. Use of excised human skin. J. Pharm. Sci. 75:1094-1097.

Bronaugh, R.L.; Stewart, R.F.; Storm, J.E. (1989) Extent of cutaneous metabolism during percutaneous absorption of xenobiotics. Toxicol. Appl. Pharmacol. 99:534-543.

Brown, H.A.; Hattis, D. (1989) The role of skin absorption as a route of exposure to volatile organic compounds in household tap water: a simulated kinetic approach. J. Am. Coll. Toxicol. 8(5):839-851.

Brown, H.S.; Bishop, D.R.; Rowan, C.A. (1984) The role of skin absorption as a route of exposure for volatile organic compounds (VOCs) in drinking water. Am. J. Public Health 74(5):479-484.

Brown, R.; Cofone, L.; Diwan, I.; Mittelman, A.; Hoang, K.; Schaum, J. (1990) Ability of theoretical skin permeability models to predict permeability coefficient or flux values for environmental pollutants. Presented at: Principles of Route-to-Route Extrapolation Meeting; March 1990; Hilton Head, SC.

Bucks, D.; Guy, R.H.; Maibach, H.I. (1991) Effects of occlusion. In: Bronaugh, R.L.; Maibach, H.I., eds. In vitro percutaneous absorption: principles, fundamentals and applications. Boca Raton, FL: CRC Press; pp. 85-114.

Burmaster, D.E.; Maxwell, N.I. (1991) Time and loading - dependence in the Mckone model for dermal uptake of organic chemicals from a soil matrix. Risk Analysis. 11:491-497.

Casarett, L.J.; Doull, J. (1986) Toxicology: the basic science of poisons. 3rd ed. New York, NY: Macmillan Publishing Company. pp. 415.

Chellquist, E.M.; Reifenrath, W.G. (1988) Distribution and fate of diethyl malonate and diisopropyl fluorophosphate on pig skin in vitro. J. Pharm. Sci. 77(10):850-854.

Chen, C.; Hoang, K. (1992, In press) Incorporation of biological information in CRA and issues related to high background tumor incidence rate. In: Wang, R.; Knaak, J.; Maibach, H., eds. Health risk assessment through dermal and inhalation exposure and absorption of toxicants. Boca Raton, Fl: CRC Press.

Chien, Y.W.; Chien, T.Y.; Bagdon, R.E.; Huang, Y.C.; Bierman, R.H. (1989) Transdermal dual-controlled delivery of contraceptive drugs. Pharm. Res. 6(12):1000-1010.

Chowhan, Z.T.; Pritchard, R. (1978) Naproxin. I. Comparison of rabbit, rat and human skin. J. Pharm. Sci. 67:1272-1274.

Cleek, R.L.; Bunge, A.L. (1992) A new method for estimating dermal absorption from chemical exposure. Submitted.

Clewell, H.J.; Haddad, T.S.; Fazekas, T.E.; McDougal, J.N.; Andersen, M.E. (1988) Dermal absorption of 1,1-dimethylhydrazine (UDMH) vapor. Presented at: 1988 Jannaf Safety and Environmental Protection Subcommittee Meeting; May 1988; Monterey, CA.

Clenddening, W.E.; Stoughton, R.R. (1962) Importance of the aqueous/lipid partition coefficient for percutaneous absorption of weak electrolytes. J. Invest. Dermatol. 39:47.

Collier, S.W.; Sheikh, N.M.; Sakr, A.; Lichtin, J.L.; Stewart, R.F.; Bronaugh, R.L. (1989a) Maintenance of skin viability during in vitro percutaneous absorption/metabolism studies. Toxicol. Appl. Pharmacol. 99:522-533.

Collier, S.W.; Storm, J.E.; Bronaugh, R.L. (1989b) Structure-related differences in the metabolic rate of aniline during color metabolism in sencoar mouse skin. Toxicol. 9:164.

Corbo, M.; Wang, P.R.; Li, J.K.J.; Chien, Y.W. (1989) Effect of propanol on the myocardial contractility of normotensive and sponstaneously hypertensive rabbits: relationship of pharmacokinetics and pharmacodynamics. J. Pharmacokinet. Biopharm. 17(5):551-570.

Corbo, M.; Liu, J.C.; Chien, Y.W. (1990) Bioavailability of propanol following oral and transdermal administration in rabbits. J. Pharm. Sci. 79(7):584-587.

Crank, J.C. (1975) The mathematics of diffusion. Oxford U.K.: Clarendon Press.

Cussler, E.L. (1984) Diffusion - mass transfer in fluid systems. New York, NY: Cambridge University Press.

Dahl R. (1990) Contemporary issues in toxicology dose concepts for inhaled vapors and gases. Toxicol. Appl. Pharmacol. 103:185-197.

Dal Pozzo, A.; Donzelli, G.; Liggeri, E.; Rodriguez L. (1991) Percutaneous absorption of nicotinic acid derivatives in vitro. J. Pharm. Sci. 80(1):54-57.

DelTerzo, S.; Behl, C.R.; Nash, R.A.; Bellantone, N.H.; Malick, A.W. (1986) Evaluation of the nude rat as a model: effects of short-term freezing and alkyl chain length on the permeabilities of n-alkanols and water. J. Soc. Cosmet. Chem. 37:297-307.

DHHS (U.S. Department of Health and Human Services) Occupational Health Guidelines for Chemical Hazards. (1981) HHS, DOL, CDC and OSHA. Washington, DC.

DHHS (U.S. Department of Health and Human Services) Occupational Health Guidelines for Chemical Risks. (1983) National Library of Medicine, Bethesda, Maryland.

DOI (U.S. Department of Interior). (1973) Outdoor recreation: a legacy for America. U.S. Department of Interior, Washington, DC. Available from DOI.

DOT (U.S. Department of Transportation) (1990). Emergency response guidebook. Available from GPO, Washington, DC. S/N 050-000-00-534-8.

Driver, J.H.; Konz, J.J.; Whitmyre, G.K. (1989) Soil adherence to human skin. Bull. Environ. Contam. Toxicol. 43:814-820.

DuBois, D.; DuBois, G.F. (1916) A formula to estimate the approximate surface area if height and weight be known. Arch. Intern. Med. 17:863-871.

Dugard, P.H. (1986) Absorption through the skin: theory, in vitro techniques and their applications. Food Chem. Toxicol. 24(6/7):749-753.

Dugard, P.H.; Walker, M.; Mawdsley, S.J.; Scott, R.C. (1984) Absorption of some glycol ethers through human skin in vitro. Environ. Health Perspect. 57:193-197.

Dupuis, D.; Rougier, A.; Roguet, R.; Lotte, C. (1986) The measurement of the stratum corneum reservoir: a simple method to predict the influence of vehicles on in vivo percutaneous absorption. Br. J. Dermatol. 115:233-238.

Durham, W.F.; H.R. Wolfe. (1962) Measurement of the exposure of workers to pesticides. Bull WHO 26:75-91.

Durrheim, H.; Flynn, G.L.; Higuchi, W.I.; Behl, C.R. (1980) Permeation of hairless mouse skin: I. experimental methods and comparison with human epidermal permeation by alkanols. J. Pharm. Sci. 69:781-786.

Dutkiewicz, T.; Piotrowski, J. (1961) Experimental investigations on the quantitative estimation of aniline absorption in man. Pure Appl. Chem. 3:319-323.

Dutkiewicz, T.; Tyras, H. (1967) A study of the skin absorption of ethylbenzene in man. Br. Med. J. 24:330-332.

Dutkiewicz, T.; Tyras, H. (1968) Skin absorption of toluene, styrene, and xylene by man. Br. J. Ind. Med. 25:243-246.

Elias, P.M.; Cooper, E.R.; Korc, A.; Brown, B.E. (1981) Percutaneous transport in relation to stratum corneum structure and lipid composition. J. Invest. Dermatol. 76:297-301.

Elias, P.M.; Feingold, K.R.; Menon, G.K.; Grayson, S.; Williams, M.L.; Grubauer, G. (1987) The stratum corneum two-compartment model and its functional implications. In: Shroot B.; Schaefer, H., eds. Pharmacology and the skin. v. 1, Skin pharmacokinetics. Basel, Switzerland: Karger, pp. 2-1 pp. 1-9.

Engstrom, K.; Husman, K.; Riihimaki, V. (1977) Percutaneous absorption of m-xylene in man. Int. Arch. Occup. Environ. Health 39:181-189.

EPA (U.S. EPA) (1983) Methods for assessing exposure to chemical substances. v. 3, Methods for assessing exposure criteria from disposal of chemical substances. Office of Toxic Substances, Washington, DC. EPA/560/5-83-016. Available from NTIS, Springfield, VA; PB-86-107059.

EPA (U.S. EPA) (1984a) Pesticide assessment guidelines subdivision K, exposure: reentry protection. Office of Pesticide Programs, Washington, DC. EPA/540/9-48/001. Available from NTIS, Springfield, VA; PB-85-120962.

EPA (U.S. EPA) (1984b) Risk analysis of TCDD contaminated soil. Office of Health and Environmental Assessment, Exposure Assessment Group, Washington, DC. EPA/600/8-84/031. Available from NTIS, Springfield, VA; PB-85-145704.

EPA (U.S. EPA) (1984c) Techniques for the assessment of the carcinogenic risks to the U.S. population due to exposure from selected volatile organic compounds from drinking water via ingestion, inhalation and dermal routes. Office of Drinking Water, Washington, DC. EPA/570/9-85/001. Available from NTIS, Springfield, VA; PB-84-213941.

EPA (U.S. EPA) (1985) Development of statistical distributions or ranges of standard factors used in exposure assessments. Office of Health and Environmental Assessment, Exposure Assessment Group, Washington, DC. EPA/600/8-85/010. Available from NTIS, Springfield, VA; PB-85-242667/AS.

EPA (U.S. EPA) (1986) Pesticide assessment guidelines subdivision U, applicator exposure monitoring. Office of Pesticide Programs, Washington, DC. EPA/540/9-87/127. Available from NTIS, Springfield, VA; PB-85-133286.

EPA (U.S. EPA) (1987a) Selection criteria for mathematical models used in exposure assessments: surface water models. Exposure Assessment Group, Office of Health and Environmental Assessment, Washington, DC. EPA/600/8-87/042. Available from NTIS, Springfield, VA; PB-88-139928/AS.

EPA (U.S. EPA) (1987b) The risk assessment guidelines of 1986. Office of Research and Development, Office of Health and Environmental Assessment, Washington, DC. EPA/600/8-87/045. Available from NTIS , Springfield, VA; P-88-123997/AS.

EPA (U.S. EPA) (1988a) Estimating exposure to 2,3,7,8-TCDD. Office of Health and Environmental Assessment, Washington, DC. EPA/600/6-88/005A. Available from NTIS, Springfield, VA; PB-88-231196/AS.

EPA (U.S. EPA) (1988b) Superfund exposure assessment manual. Office of Emergency and Remedial Response, Washington, DC. EPA/540/1-88/001. Available from NTIS, Springfield, VA; PB-89-135859.

EPA (U.S. EPA) (1988c) Selection criteria for mathematical models used in exposure assessments: groundwater models. Exposure Assessment Group, Office of Health and Environmental Assessment, Washington, DC. EPA/600/8-88/075. Available from NTIS, Springfield, VA; PB-88-248752/AS.

EPA (U.S. EPA) (1989a) Exposure factors handbook. Office of Health and Environmental Assessment, Exposure Assessment Group, Washington, DC. EPA/600/8-89/043. Available from NTIS, Springfield, VA; PB-90-106774/AS.

EPA (U.S. EPA) (1989b) Risk assessment guidance for superfund. Human health evaluation manual: part A. Interim Final. Office of Solid Waste and Emergency Response, Washington, DC. Available from NTIS, Springfield, VA; PB-90-155581.

EPA (U.S. EPA) (1990a) Guidelines for exposure assessment. SAB Draft Final. Office of Research and Development. Office of Health and Environmental Assessment. Available from Exposure Assessment Group, Washington, DC., August 8, 1991. OHEA-E-451.

EPA (U.S. EPA) (1990b) Integrated risk information system (IRIS). On-line. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

EPA (U.S. EPA) (1990c) Interim methods for development of inhalation reference concentrations (Ext. review draft). Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, N.C. EPA/600/8-90/066A. Available from NTIS, Springfield, VA; PB-90-238890.

EPA (U.S. EPA) (1990d) Methodology for assessing health risks associated with indirect exposure to combustor emmissions. EPA 600/6-90/003. Available from NTIS, Springfield, VA; PB-90-187055/AS.

EPA (U.S. EPA) (1990e) Principles of route-to-route extrapolation for risk assessment. In: Gerrity, T.R., Henry C.J., eds. Proceedings of the Workshops on Principles of Route-to-Route Extrapolation for Risk Assessment; March 1990 in Hilton Head, South Carolina and July 1990 in Durham, North Carolina. New York, NY: Elsevier Press.

EPA (U.S. EPA) (1990f) Non-occupational pesticide exposure study. (NOPES). Atmospheric Research and Exposure Assessment Laboratory, Research Triangle Park, NC: EPA/600/3-90-003. Available from NTIS, Springfield, VA; PB-90152224.

EPA (U.S. EPA) (1991) Percutaneous absorption of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and 3,3'4,4'-tetrachlorobiphenyl (TCB) applied in soil. Office of Health and Environmental Assessment. Available from Exposure Assessment Group, Washington, DC. OHEA-E-453.

Eschenroeder, A.; Jaeger, R.J.; Ospital, J.J.; Doule, C.P. (1986) Health risk analysis of human exposures to soil amended with sewage sludge contaminated with polychlorinated dibenzo-p-dioxins and dibenzofurans. Vet. Hum. Toxicol. 28(5):435-442.

Faredin, I.; Toth, I.; Fazekas, A.; Kokai, K.; Julesz, M. (1968) Conjugation in vitro of (4-14C) dehydroepiandrosterone to (4-14C) dehydroepiandrosterone sulfate by normal human female skin slices. J. Endocrinol. 41:295-296.

Feldmann, R.J., Maibach, H.I. (1967) Regional variation in percutaneous penetration of ^{14}C cortisol in man. J. Invest. Dermatol. 48(2):181-183.

Feldmann, R.J.; Maibach, H.I. (1969) Percutaneous penetration of steroids in man. J. Invest. Dermatol. 52:89-94.

Feldmann, R.J.; Maibach, H.I. (1970) Absorption of some organic compounds through the skin in man. J. Invest. Dermatol. 54:399-404.

Feldmann, R.J.; Maibach, H.I. (1974) Percutaneous penetration of some pesticides and herbicides in man. Toxicol. Appl. Pharmacol. 28:126-132.

Fenske, R.A. (1988) Comparative assessment of protective clothing performance by measurement of dermal exposure during pesticide application. Appl. Ind. Hyg. 7(3):207-213.

Fenske, R.A.; Leffingwell, J.T.; Spear, R.C. (1985) Evaluation of fluorescent tracer methodology for dermal exposure assessment. In: Honeycutt, R.C.; Zweig, G.; Ragsdale, N., eds. Dermal exposure related to pesticide use. ACS Symposium Series No. 273. American Chemical Society, Washington, DC; pp. 377-393.

Fenske, R.A.; Leffingwell, J.T.; Spear, R.C. (1986) A video imaging technique for assessing dermal exposure. II. Fluorescent tracer testing. Am. Ind. Hyg. Assoc. J. 47:771-775.

Fisher, A.A. (1967) Contact dermatitis. Philadelphia, PA: Lea and Febiger Publishers.

Flynn. G.L. (1985) Mechanism of percutaneous absorption from physicochemical evidence. In: Bronaugh, R.; Maibach, H.I., eds. Percutaneous absorption: mechanisms—methodology—drug delivery. New York, NY: Marcel Dekker; pp. 17-42.

Flynn, G.L. (1989) Mechanism of percutaneous absorption from physicochemical evidence. In: Bronaugh, R.; Maibach, H.I., eds. Percutaneous absorption: mechanisms—methodology—drug delivery, 2nd ed., New York, NY: Marcel Dekker; pp. 27-51.

Flynn, G.L. (1990) Physiochemical determinants of skin absorption. In: Gerity, T.R.; Henry, C.J., eds. Principles of route-to-route extrapolation for risk assessment. Amsterdam: Elsevier Science Publishing Co. Inc; pp. 93-127.

Flynn, G.L. (1991) In: Swarbrick, J.; Boylan, J.C., eds. Encyclopedia of pharmaceutical technology: v.3. New York, NY: Marcel Dekker, Inc.; pp. 457-503.

Flynn, G.L.; Stewart, B. (1988) Percutaneous drug penetration: choosing candidates for transdermal development. Drug Dev. Res. 13:169-185.

Flynn, G.L.; Durrheim, H.; Higuchi, W.I. (1980) Permeability of hairless mouse skin. II. Membrane sectioning techniques and influence on alkanol permeabilities. J. Pharm. Sci. 70(1):52-56.

Fox, C.; Selkirk, J.; Price, F.; Croy, R.; Sanford, K.; Fox, M. (1975) Metabolism of benzo(a) pyrene by human epithelial cells in vivo. Cancer Res. 35:3551-3557.

Franklin, C.A.; Somers, D.A.; Chu, I. (1989) Use of percutaneous absorption data in risk assessment. J. Amer. Coll. Toxicol. 8(5):815-827.

Franz, T.J. (1975) Percutaneous absorption: On the relevance of in vitro data. J. Invest. Dermatol. 64(3):190-195.

Franz, T.J. (1978) The finite dose technique as a valid in vitro model for the study of percutaneous absorption in man. Curr. Probl. Dermatol. 7:58-68.

Franz, S.W. (1990) Instrumentation and methodology for in vitro skin diffusion cells. In: Kemppainen B.W.; Reifenrath, W.G., eds. Methodology for skin absorption. Boca Raton, FL: CRC Press; pp 35-59.

Franz, S.W.; Dittenber, D.A.; Eisenbrandt, D.L.; Watanabe, P.G. (1990) Evaluation of a flow-through in vitro skin penetration chamber method using acetone-deposited organic solids. J. Toxicol. Cut. Ocular Toxicol. 9:277-299.

Frederiksson, T. (1961a) Studies of the percutaneous absorption of parathion and paraoxon. V. Rate of absorption of paraoxon. J. Invest. Dermatol. 8:233-236.

Frederiksson, T. (1961b) Studies of the percutaneous absorption of parathion and paraoxon. III. Rate of absorption of parathion and paraoxon. Acta Derm. Venereol. 41:353-362.

Frederiksson, T. (1962) Studies of the percutaneous absorption of parathion and paraoxon. V. Rate of absorption of paraoxon. J. Invest. Dermatol. 38:233-236.

Friberg, L.; Skog, E.; Wahlberg, J.E. (1961) Resorption of mercuric chloride and methyl mercury dicyandiamide in guinea-pigs through normal skin and through skin pretreated with acetone, alkylaryl sulphonate and soap. Acta Derm. Venereol. 41:40-52.

Fries, G.F.; Marrow, G.S. (1975) Retention and excretion of 2,3,7,8-tetrachlorodibenzo-p-dioxin by rats. J. Agric. Food Chem. 23:265.

Fujimoto, S.; Watanabe, T. (1969) Studies on the body surface area of Japanese. Acta Medica Nagasaki, Japan, 13:1-13.

Fullerton, A.; Andersen, J.R.; Hoelgaard, A.; Menné, T. (1986) Permeation of nickel salts through human skin in vitro. Contact Derm. 15:173-177.

Fullerton, A.; Andersen, J.R.; Hoelgaard, A. (1988) Permeation of nickel through human skin in vitro - effect of vehicles. Br. J. Dermatol. 118:509-516.

Garcia, B.; Marty, J.; Wepierre, J. (1980) Etude des facteurs conditionnant l'absorption percutanee des alcools incorpores dans des melanges eau-monooleate de sorbetanne polyoxyethylene-myristate d-isopropyle. Int. J. Pharmaceut. 4:205-217.

Gargas, M.L.; Burgess, R.J.; Voisard, D.E.; Cason, G.H.; Andersen, M.E. (1989) Partition coefficients of low-molecular-weight volatile chemicals in various liquids and tissues. Toxicol. Appl. Pharmacol. 98:87-89.

Grasso, P.; Lansdown, A.B.G. (1972) Methods of measuring, and factors affecting, percutaneous absorption. J. Soc. Cosmet. Chem. 23:481-521.

Grissom, R.E.; Brownie, C.; Guthrie, F.E. (1987) In vivo and in vitro dermal penetration of lipophilic and hydrophilic pesticides in mice. Bull. Environ. Contam. Toxicol. 38:917-924.

Guest, D.; Hamilton, M.L.; Deisinger, P.J.; Divincenzo, G.D. (1984) Pulmonary and percutaneous absorption of 2-propoxyethyl acetate and 2-ethoxyethyl acetate in beagle dogs. Environ. Health Perspect. 57:177-183.

Gummer, C.; Maibach, H.I. (1991) Diffusion cell design. In: Bronaugh, R.L.; Maibach, H.I. eds. In vitro percutaneous absorption principles, fundamentals and applications. Boston, MA: CRC press, pp. 7-16.

Guy, R.H. (1989) Developing predictive models of Percutaneous absorption. I. Transport of Phenols. Submitted to Office of Health Environmental Assessment; US EPA under Cooperative Agreement CR-812474. University of California, San Francisco, School of Pharmacy.

Guy, R.H.; Hadgraft, J. (1984) Prediction of drug disposition kinetics in skin and plasma following topical application. J. Pharm. Sci. 73:883-887.

Guy, R.H.; Hadgraft, J. (1988) Physiochemical aspects of percutaneous penetration and its enhancement. Pharm. Res. 5(12):753-758.

Guy, R.H.; Hadgraft, J. (1989a) Mathematical models of percutaneous absorption. In: Bronaugh, R.L.; Maibach, H.I., eds. Percutaneous absorption. New York, NY: Marcel Dekker; pp. 13-26.

Guy, R.H.; Hadgraft, J. (1989b) Structure-activity correlations in percutaneous absorption. In: Bronaugh, R.L.; Maibach, H.I., eds. Percutaneous absorption. New York, NY: Marcel Dekker; pp. 95-109.

Guy, R.H.; Maibach, H.I. (1984) Correction factors for determining body exposure from forearm percutaneous absorption data. J. Appl. Toxicol. 4(1):26-28.

Guy, R.H.; Hinz, R.S.; Amantea, M. (1984) Solute transport and perturbation at liquid/liquid interfaces. Faraday Discuss. Chem. Soc. 77:127-137.

Guy, R.H.; Tur, E.; Maibach, H.I. (1985) Optical techniques for monitoring cutaneous microcirculation. Int. J. Dermatol. 24:88-94.

Hadgraft, J. (1983) Percutaneous absorption: possibilities and problems. Inter. J. Pharm. 16: 255-270.

Hadgraft, J.; Ridout, G. (1987) Development of model membranes for percutaneous absorption measurements: I. isopropyl myristate. Int. J. Pharm. 39:149-156.

Hadgraft, J.; Ridout, G. (1988) Development of model membranes for percutaneous absorption measurements: II. dipalmitoyl phosphatidylcholine, linoleic acid and tetradecane. Int. J. Pharm. 42:97-104.

Håkanson, R.; Moller, H. (1963) On metabolism of noradrenaline in the skin: activity of catechol-o-methyl transferase and monoamine oxidase. Acta. Dermato-Venereologica. 43:552-555.

Hall, L.C.; Bogen, K.T.; McKone, T.E.; Mallon, B.; Hall, C.H. (1989) Health risk assessment of trans-1,2-Dichloroethylene. Lawrence Livermore Laboratory, Livermore, CA; UCRL-21062. Available from NTIS, Springfield, VA; DE-89-007229.

Hanke, J.; Dutkiewicz, T.; Piotrowski, J. (1961) The absorption of benzene through human skin. Med. Pr. 12:413-426. (in Polish; English summary).

Hansch, C.; Leo, A. (1979) Substituent constants for correlations in chemistry and biology. New York, NY: Wiley-Interscience.

Harper, K.; Calcutt, G. (1960) Conjugation of 3:4-benzpyrenols in mouse skin. Nature 186:80-81.

Hawkins, G.S.; Reifenrath, W.G. (1984) Development of an in vitro model for determining the fate of chemicals applied to skin. Fundam. Appl. Toxicol. 4:S133-S144.

Hawkins, G.S.; Reifenrath, W.G. (1986) Influence of skin source, penetration cell fluid, and partition coefficient on in vitro skin penetration. J. Pharm. Sci. 75(4):378-381.

Hawley, J.K. (1985) Assessment of health risk from exposure to contaminated soil. Risk Anal. 5:289-302.

Hefner R.E.; Watanabe P.G.; Gehring P.J. (1975) Short communication perutaneous absorption of vinyl chloride. Toxicol. Appl. Phamacol. 34:529-532.

Holland, J.M.; Kao, J.Y.; Whitaker, M.J. (1984) A multisample apparatus for kinetic evaluation of skin penetration in vitro: the influence of viability and metabolic status of the skin. Toxicol. App. Pharmacol. 72:272-280.

Houk, J.; Guy, R.H. (1988) Membrane models for skin penetration studies. Chem. Rev. 88(3):455-471.

Huq, A.S.; Ho, N.F.; Huisari, N.; Flynn, G.L.; Jetzer, W.E.; Condie, L., Jr. (1986) Permeation of water contaminative phenols through hairless mouse skin. Arch. Environ. Contam. Toxicol. 155:557-566.

Hursh, J.B.; Clarkson, T.W.; Miles, E.F.; Goldsmith, L.A. (1989) Percutaneous absorption of mercury vapor by man. Arch. Environ. Health 44(2):120-127.

Idson, B.; Behl, C.R. (1987) In: Kydonieus, A.F.; Berner, B., eds. Transdermal delivery of drugs, v.3. Boca Raton, FL: CRC Press; p 85.

James, I.R.; Knuiman, M.W. (1987) An application of Bayes methodology to the analysis of diary records from a water use study. J. Am. Stat. Assoc. 82(399):705-711.

Jarabek A.M.; Menache M.G.; Overton J.M.; Dourson, M.L.; Miller, F.J. (1990) The U.S. Environmental Protection Agency's inhalation RFD methodology: risk assessment for air toxics. Toxicol. Ind. Health 6(5):279-301.

Jetzer, W.E.; Huq, A.S.; Ho, N.F.; Flynn, G.L.; Duraiswamy, N.; Condie, L., Jr. (1986) Permeation of mouse skin and silicone rubber membranes by phenols: relationship to in vitro partitioning. J. Pharm. Sci. 75(11):1098-1103.

Jetzer, W.E.; Hou, S.Y.E.; Huq, A.S.; Duraiswamy, N.; Ho, N.H.; Flynn, G.L. (1988) Temperature dependency of skin permeation of waterborne organic compounds. Pharm. Acta Helv. 63:197-201.

Jo, W.K.; Weisel, C.D.; Lioy, P.J. (1990a) Chloroform exposure and the health risk associated with multiple uses of chlorinated tap water. Risk Anal. 10(4):581-585.

Jo, W.K.; Weisel, C.P.; Lioy, P.J. (1990b) Routes of chloroform exposure and body burden from showering with chlorinated tap water. Risk Anal. 10(4):575-580.

Johanson, G.; Fernstrom, P. (1986) Percutaneous uptake rate of 2-butoxyethanol in guinea pigs. Scand. J. Work Environ. Health 12:499-503.

Johanson, G.; Fernstrom, P. (1988) Influence of water on the percutaneous absorption of 2-butoxyethanol in guinea pigs. Scand. J. Work Environ. Health 14:95-100.

Johanson, G.; Boman, A.; Dynesius, B. (1988) Percutaneous absorption of 2-butoxyethanol in man. Scand. J. Work Environ. Health 14:101-109.

Kao, J.; Hall, J.; Shugart, L.R.; Holland, J.M. (1984) An in vitro approach to studying cutaneous metabolism and disposition of topically applied xenobiotics. Toxicol. Appl. Pharmacol. 75:289-298.

Kao, J.; Patterson, F.K.; Hall, J. (1985) Skin penetration and metabolism of topically applied chemicals in six mammalian species, including man: an in vitro study with benzo[a]pyrene and testosterone. Toxicol. Appl. Pharmacol. 81:502-516.

Kao, J.; Hall, J.; Helman, G. (1988) In vitro percutaneous absorption in mouse skin: Influence of skin appendages. Toxicol. Appl. Pharmacol. 94:93-103.

Kasting, G.B.; Smith, R.L.; Cooper, E.R. (1987) Effect of lipid solubility and molecular size on percutaneous absorption. Pharmacol. Skin 1:138-153.

Katz, M.; Shaikh, Z.I. (1965) Percutaneous corticosteroid absorption correlated to partition coefficient. J. Pharm. Sci. 54:591.

Kawakubo, Y.; Manabe, S.; Yamazoe, Y.; Nishikawa, T.; Kato, R. (1988) Properties of cutaneous acetyltransferase catalyzing N- and O-acetylation of carcinogenic arylamines and N-hydroxyarylamine. Biochem. Pharmacol. 37(2):265-270.

Keshary, P.; Chien, Y. (1984) Mechanism of transdermal controlled nitroglycerin administration: II. Assessment of rate-controlling steps. Drug Dev. Ind. Pharmacy 10:1663-1669.

Kimbrough, R.D.; Falk, H.; Stehr, P.; Fries, G. (1984) Health implications of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) contamination of residential soil. J. Toxicol. Environ. Health 14:47-93.

Kissel, J.C.; McAvoy, D.R. (1988) Estimating dermal absorption from soil using the fugacity approach. Proceedings of the 9th National Conference on Superfund '88. Nov. 28-30; Washington, DC. Hazardous Materials Control Research Institute.

Kissel, J.C.; McAvoy, D.R. (1989) Reevaluation of the dermal bioavailability of 2,3,7,8-TCDD in soil. Haz. Waste Haz. Materials 6:231-240.

Knaak, J.B.; Yee, K.; Ackerman, C.R.; Zweig, G.; Wilson, B.W. (1984a) Percutaneous absorption of triadimefon in the adult and young male and female rat. Toxicol. Appl. Pharmacol. 72:406-416.

Knaak, J.B.; Yee, K.; Ackerman, C.R.; Zweig, G.; Fry, D.M.; Wilson, B.W. (1984b) Percutaneous absorption and dermal dose - Cholinesterase response studies with parathion and carbaryl in the rat. Toxicol. Appl. Pharmacol. 76:252-263.

Kohli, R.; Archer, W.I.; LiWan, P.A. (1987) Laser velocimetry for the non-invasive assessment of the percutaneous absorption of nicotinates. Int. J. Pharm. 36:91-98.

Komatsu, H.; Suzuki, M. (1982) Studies on the regeneration of the skin barrier and the changes in ^{32}P incorporation into the epidermis after stopping. Br. J. Dermatol. 106:551-560.

Lepow, M.L.; Bruckman, L.; Gillette, M.; Markowitz, S.; Rubino, R.; Kapish, J. (1975) Investigations into sources of lead in the environment of urban children. Environ. Res. 10:415-426.

Lien, E.J.; Tong, G.L. (1973) Physicochemical properties and percutaneous absorption of drugs. J. Soc. Cosmet. Chem. 24:371-384.

Liron, Z.; Cohen, S. (1984a) Percutaneous absorption of alkanoic acids. I. A study of operational conditions. J. Pharm. Sci. 73(4):534-537.

Liron, Z.; Cohen, S. (1984b) Percutaneous absorption of alkanoic acids. II. Application of regular solution theory. J. Pharm. Sci. 73(4):538-542.

Lopp, A.; Shevchuk, I.; Kirso, U. (1986) Fluorescence methods for the measurements of penetration and metabolism of carcinogens in mouse skin. Cancer Biochem. Biophys. 8:185-191.

Lyman, W.J.; Reehl, W.F.; Rosenblatt, D.H. (1982) Handbook of chemical property estimation methods. New York, NY: McGraw-Hill Book Company.

Mackay, D.; Paterson, S. (1981) Calculating fugacity. Environ. Sci. Tech. 15:1006-1014.

Mackay, D.; Paterson, S. (1982) Fugacity revisited. Environ. Sci. Tech. 16:654A-660A.

Maddy, K.T.; Wang, R.G.; Winter, C.K. (1983) Dermal exposure monitoring of mixers, loaders and applicators of pesticides in California. Worker Health and Safety Unit, Report HS-1069, California Department of Food and Agriculture, Sacramento, CA.

Maibach, H.I. (1989) Comments on presentations by speakers at symposium I. J. Am. Coll. Toxicol. 8(5):861-862.

Maibach, H.I.; Feldmann, R.J.; Milby, T.H.; Serat, W.F. (1971) Regional variation in percutaneous penetration in man. Arch. Environ. Health 23:208-211.

Marks, R.M.; Barton, S.P.; Edwards, C., eds. (1988) The physical nature of the skin. Lancaster, PA: MTP Press, Ltd.

Marzulli, F.N. (1962) Barriers to skin penetration. J. Invest. Dermatol. 39:397-393.

Marzulli, F.N.; Maibach, H.I. (1984) Permeability and reactivity of skin as related to age. J. Soc. Cosmet. Chem. 35: 95-102.

Marzulli, F.N.; Maibach, H.I., eds. (1991) Dermatotoxicology. 4th ed. Washington, DC.: Hemisphere Publishing Co.

Marzulli, F.N.; Brown, D.W.; Maibach, H.I. (1969) Techniques for studying skin penetration. Toxicol. Appl. Pharmacol. 3(suppl):76-83.

McDougal, J.N. (1991) Physiologically-based pharmacokinetic modeling. Dermatol. Toxicol. 37:60.

McDougal, J.N.; Jepson, G.W.; Clewell, H.J., III; MacNaughton, M.G.; Andersen, M.E. (1986) A physiological pharmacokinetic model for dermal absorption of vapors in the rat. Toxicol. Appl. Pharmacol. 85(2):286-294.

McDougal, J.N.; Jepson, G.W.; Clewell, H.J., III; Andersen, M.E. (1987) Pharmacokinetics of organic vapor absorption. Pharmacol. Skin 1:245-251.

McDougal, J.N.; Jepson, G.W.; Clewell, H.J., III; Gargas, M.L.; Andersen, M.E. (1990) Dermal absorption of organic chemical vapors in rats and humans. Fundam. Appl. Toxicol. 14:299-308.

McGreesh, A.H. (1965) Percutaneous toxicity. Toxicol. Appl. Pharmacol. 2(suppl):20-26.

McKone, T.E. (1987) Human exposure to volatile organic compounds in household tap water: the indoor inhalation pathway. Environ. Sci. Technol. 21:1194-1201.

McKone, T.E. (1990) Dermal uptake of organic chemicals from a soil matrix. Risk Anal. 10(3):407-419.

McKone, T.E.; Layton, D.W. (1986) Screening the potential risks of toxic substances using a multimedia compartment model: Estimation of human exposure. Regul. Toxicol. Pharmacol. 6:359-380.

Merck Index. (1989) An encyclopedia of chemicals, drugs, and biologicals. 11th ed. Budavari, S., ed. Rathway, NJ: Merck and Co., Inc.

Michaels, A.S.; Chandrasekaran, S.K.; Shaw, J.E. (1975) Drug permeation through human skin: Theory and in vitro experimental measurement. Am. Inst. Chem. Eng. J. 21(5):985-996.

Monteiro-Rivierie, N.; Banks, Y.; Birnbaum, L. (1991) Laser doppler measurements of cutaneous blood flow in ageing mice and rats. Toxicol. letter. Submitted.

Moody, R.; Riedel, D.; Ritter, L.; Franklin, C., (1987) The effect of DEET (N,N-diethyl-m-toluamide) on dermal persistence and absorption of the insecticide fenitrothion in rats and monkeys. J. Toxicol. Environ. Health 22:471-479.

Moore, M.R.; Meredith, P.A.; Watson, W.S.; Sumner, D.J.; Taylor, M.K.; Goldberg, A. (1980) The percutaneous absorption of lead-203 in humans from cosmetic preparations containing lead acetate, as assessed by whole-body counting and other techniques. Food Cosmet. Toxicol. 18:399.

Nathan, D.; Sakr, A.; Litchtin, J.L.; Bronaugh, R.L. (1990) In vitro skin absorption and metabolism of benzoic acid, *p*-aminobenzoic acid and benzocaine in the hairless guinea pig. Pharmaceut. Res. 7:1147-1151.

NCHS (National Center for Health Statistics) (1983) National Health and Nutrition Examination Survey 1976 - 1988, Hyattsville, MD (cited in EPA, 1985).

Noonan, P.K.; Wester, R.C. (1989) Cutaneous metabolism of xenobiotics. In: Bronaugh R.L.; Maibach H.I., eds. Percutaneous absorption. New York, NY: Marcel Dekker; pp. 53-75.

Norgaard, O. (1954) Investigations with radioactive Ag^{111} into the resorption of silver through human skin. Acta Derm. Venereol. 34:415.

OSHA (Occupational Safety and Health Administration) (1990) O-S-H-A: Permissible Exposure Limits. GPO, Washington, DC.

O'Connor, R. (1977) Fundamentals of chemistry. 2nd ed. New York, NY: Harper and Row; pp. 313-315.

Overton, J.H.; Miller F.J. (1988) Absorption of inhaled reactive gases. In: Gardner, D.E.; Crapo, J.D.; Massaro, E.J. eds. Toxicology of the lung. New York, NY: Raven Press; pp. 477-507.

Osborne, D.W. (1986) Computational methods for predicting skin permeability. Pharmaceut. Manuf. 3:41-48.

Patty's Industrial Hygiene and Toxicology. 3rd ed. (1978) Clayton, G.D.; Clayton, F.E., eds. New York, NY: John Wiley and Sons.

Paustenbach, D.P.; Shu, H.P.; Murray, F.J. (1986) A critical examination of assumptions used in risk assessments of dioxin contaminated soil. Regul. Toxicol. Pharmacol. 6:284-307.

Peck, C.C.; Lee, K.; Becker, C.E. (1981) Continuous transepidermal drug collection: basis for use in assessing drug intake and pharmakokinetics. J. Pharmacokin. Biopharm. 9:41-57.

Piotrowski, J. (1957) Quantitative estimation of aniline absorption through the skin in man. J. Hyg. Epidemiol. Microbiol. Immunol. 23:1.

Piotrowski, J. (1967) Further investigations on the evaluation of exposure to nitrobenzene. Br. J. Ind. Med. 24:60-65.

Piotrowski, J. (1971) Evaluation of exposure to phenol: absorption of phenol vapour in the lungs and through the skin and excretion of phenol in urine. Br. J. Ind. Med. 28:172-178.

Pohl, R.; Philpot, R.; Fouts, J. (1976) Cytochrome P-450 content and mixed function oxidase activity in microsomes isolated from mouse skin. Drug Metab. Dispos. 4:442-450.

Poiger, H.; Schlatter, C.H. (1980) Influence of solvents and adsorbents on dermal and intestinal absorption of TCDD. Food Cosmet. Toxicol. 18:477-481.

Potts, R.O.; Francoeur. M.L. (1991) The influence of strateum corneum morphology on water permeability. J. Invest. Dermatol. 96:495-499.

Potts R.O.; Guy R. H. (1992) Predicting skin permeability. Pharmacol. Res., accepted for publication.

Que Hee, S.S.; Peace, B.; Clark, C.S.; Boyle, J.R.; Bornschein, R.L.; Hammond, P.B. (1985) Evolution of efficient methods to sample lead sources, such as house dust and hand dust, in the homes of children. Environ. Res. 38:77-95.

Rasetti, L.; Cappellaro, F.; Gaido, P. (1961) An investigation of lead poisoning by lubricating oils containing inhibitors. Rassegna Med. Ind. Igiende Lavaro. 30:71.

Raykar, P.V.; Fung, M.C.; Anderson, B.D. (1988) The role of protein and lipid domains in the uptake of solutes by human stratum corneum. Pharm. Res. 5(3):140-150.

Reifenrath, W.G.; Robinson, P.B. (1982) In vitro skin evaporation and penetration characteristics of mosquito repellents. J. Pharm. Sci. 71:1014-1018.

Reifenrath, W.G.; Spencer, T.S. (1989) Evaporation and penetration from skin. In: Bronaugh, R.L.; Maibach, H.I., eds. Percutaneous absorption. New York, NY: Marcel Dekker; pp. 313-334.

Riihimaki, V.; Pfaffli, P. (1978) Percutaneous absorption of solvent vapors in man. Scand. J. Work Environ. Health 4:73-85.

Riley, R.T.; Kemppainen, B.W. (1985) Receptor fluid penetrant interactions and the in vitro cutaneous penetration of chemicals. In: Bronaugh R.L.; Maibach, H.I., eds. Percutaneous absorption. New York, NY: Marcel Dekker; pp. 387-392.

Riviere, J.E.; Bowman, K.F.; Monteiro-Riviere, N.A. (1985) Development of in vitro perfused porcine skin flaps for study of percutaneous absorption of xenobiotics. Report No. AD-A183-508. Annual report submitted to U.S. Army Medical Research and Development Command, Fort Detrick, MD (released 1987).

Riviere, J.E.; Bowman, K.F.; Monteiro-Riviere, N.A.; Dix, L.P.; Carver, M.P. (1986) The isolated perfused porcine skin flap (IPPSF) I. A novel in vitro model for percutaneous absorption and cutaneous toxicology studies. Fundam. Appl. Toxicol. 7:444-453.

Roberts, M.S.; Anderson, R.A.; Moore, D.E.; Swarbrick, J. (1977) The distribution of non-electrolytes between human stratum corneum and water. Australian J. of Pharm. Sci. 6:77-82.

Roels, H.A.; Buchet, J.P.; Lauwenys, R.R.; Branx, P.; Claeys-Thoreau, F.; Lafontaine, A.; Verduyn, G. (1980) Exposure to lead by oral and pulmonary routes of children living in the vicinity of a primary lead smelter. Environ. Res. 22:81-94.

Roskos, K.V.; Maibach, H.I.; Guy, R.H. (1989) The effect of aging on percutaneous absorption in man. J. Pharmacokinet. Biopharm. 17:617-629.

Rougier, A.; Dupuis, D.; Lotte, C.; Roguet, R.; Schaefer, H. (1983) In vivo correlation between stratum corneum reservoir function and percutaneous absorption. J. Invest. Dermatol. 81:275-278.

Rougier, A.; Dupuis, D.; Lotte, C.; Roguet, R. (1985) The measurement of the stratum corneum reservoir. A predictive method for in vivo percutaneous absorption studies: influence of application time. J. Invest. Dermatol. 84:66-68.

Rougier, A.; Lotte, C.; Maibach, H.I. (1987) In vivo percutaneous penetration of some organic compounds related to anatomic site in man: predictive assessment by the stripping method. J. Pharm. Sci. 76(6):451-454

Rougier, A.; DuPuis, D.; Lotte, C.; Maibach, H.I. (1989) Stripping method for measuring percutaneous absorption in vivo. In: Bronaugh R.L.; Maibach, H.I., eds. Percutaneous absorption. New York, NY: Marcel Dekker; pp. 415-434.

Roy, T.A., Yang, J.J., Czerwinski, M.H. (1987) Evaluating the percutaneous absorption of polynuclear aromatics using in vivo and in vitro techniques and structure activity relationships. In: Golberg, A.M., ed. In vitro toxicology approaches to validation. New York, NY: Mary Ann Liebert, Inc.; pp. 471.

Roy, T.A.; Yang, J.J.; Krueger, A.J.; Mackerer, C.R. (1990) Percutaneous absorption of neat 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and TCDD sorbed on soils. Toxicolology 10(1):308.

Rusch, G.M.; Leong B.K.; Laskin, S. (1977) Benzene metabolism. J. Toxicol. Environ. Health 2(suppl.):23-36.

Samitz, M.H.; Katz, S. (1976) Nickel - epidermical interactions: diffusion and binding. Environ. Res. 11:34-39.

Sato, A.; Nakajima, T. (1978) Differences following skin or inhalation exposure in the absorption and excretion kinetics of trichloroethylene and toluene. Br. J. Ind. Med. 35:43-49.

Sanders, C.L.; Skinner, C.; Gelman, R.A. (1984) Percutaneous absorption of [7,10-^{14}C]Benzo[a]pyrene and [7,12-^{14}C]Dimethylbenz[a]anthracene in mice. Environ. Res. 33:353-360.

Schaefer, H.; Lambrey, B.; Caron, D.; Illel, B.; Renucci, F. (1987) Methods in skin pharmacokinetics: introduction. In: Shroot B.; Schaefer, H., eds. Pharmacology and the skin. v. 1, skin pharmacokinetics. Basel, Switzerland: Karger, P.; pp. 50-56.

Scheuplein, R.J. (1965) Mechanism of percutaneous adsorption. I. Routes of penetration and the influence of solubility. J. Invest. Dermatol. 45:334-346.

Scheuplein, R.J. (1967) Mechanism of percutaneous absorption. II. Transient diffusion and the relative importance of various routes of skin penetration. J. Invest. Dermatol. 48(1):79-88.

Scheuplein, R.J. (1968) On the application of rate theory to complex multibarrier flow co-ordinates: membrance permeability. J. Theor. Biol. 18(1):72-89.

Scheuplein, R.J.; Blank, I.H. (1971) Permeability of the skin. Physiol. Rev. 51(4):702-747.

Scheuplein, R.J.; Blank, I.H. (1973) Mechanism of percutaneous absorption. IV. penetration of nonelectrolytes (alcohols) from aqueous solutions and from pure liquids. J. Invest. Dermatol. 60:286-326.

Scheuplein, R.J.; Blank, I.H.; Brauner, G.J.; Macfarlane, D.J. (1969) Percutaneous absorption of steroids. J. Invest. Dermatol. 52(1):63-70.

Schwartz, K.; Tulipan, L.; Birmingham, D. (1957) Occupational diseases of the skin. Philadelphia, PA: Lea and Febiger Publishers.

Scott, R.C. (1986) Chamber designs for in vitro percutaneous penetration studies. Principles and practices of in vitro percutaneous penetration studies as related to bioavailability and bioequivalence. Am. Assoc. Pharm. Sci. First National Meeting.

Scott, R.C.; Dugard, P.H. (1986) A model for quantifying absorption through abnormal skin. J. Invest. Dermatol. 86:208-213.

Scott, R.C.; Dugard, P.H. (1989) The properties of skin as a diffusion barrier and route for absorption. In: Greaves, M.W.; Shuster, S. eds. Pharmacology of the skin, v.2. New York, NY: Springer-Verlag; pp. 93-114 .

Scott, R.C.; Dugard, P.; Ramsey, J.; Rhodes, C. (1987) In vitro absorption of some o-phthalate diesters through human and rat skin. Environ. Health Perspect. 74:223-227.

Sedman, R.M. (1989) The development of applied action levels for soil contact: a scenario for the exposure of humans to soil in a residential setting. Environ. Health Perspect. 79:291-313.

Shackleford, J.M.; Yielding, K.L. (1987) Application of the fiber-optic perfusion fluorometer to absorption and exsorption studies in hairless mouse skin. Anat. Rec. 219:102-107.

Shah, P.V.; Guthrie, F.E. (1983) Dermal absorption of benzidine derivatives in rats. Bull. Environ. Contam. Toxicol. 31:73-78.

Shah, P.V.; Fisher, M.L.; Sumier, M.R.; Monroe, R.J.; Chernoff, N.; Hall, L.L. (1987) Comparison of the penetration of 14 pesticides through the skin of young and adult rats. J. Toxicol. Environ. Health 21:353-366.

Shehata, T.A. (1985) A multi-route exposure assessment of chemically contaminated drinking water. Toxicol. Ind. Health 1(4):277-298.

Shu, H.; Teitelbaum, P.; Webb, A.S.; Marple, L.; Brunck, B.; DeiRossi, D.; Murray, F.J.; Paustenbach, D. (1988) Bioavailability of soil-bound TCDD: dermal bioavailability in the rat. Fundam. Appl. Toxicol. 10:335-343.

Siddiqui, O.; Sun, Y.; Liu, J.C.; Chien, Y.W. (1987) Facilitated transdermal transport of insulin. J. Pharm. Sci. 76(4):341-345.

Skog, E.; Wahlberg, J.E. (1964) A comparative investigation of the percutaneous absorption of metal compounds in the guinea pig by means of the radioactive isotopes: ^{51}Cr, ^{58}Co, ^{65}Zn, ^{110m}Ag, ^{115m}Cd, ^{203}Hg. J. Invest. Dermatol. 43:187-192.

Skowronski, G.A.; Turkall, R.M.; Abdel-Rahman, M.S. (1988) Soil adsorption alters bioavailability of benzene in dermally exposed male rats. Am. Ind. Hyg. Assoc. J. 49:506-511.

Skowronski, G.A.; Turkall, R.M.; Abdel-Rahman. M.S. (1989) Effects of soil on percutaneous absorption of toluene in male rats. J. Toxicol. Environ. Health 26:373-384.

Skowronski, G.A.; Turkall, R.M.; Kadry, A.R.M.; Abdel-Rahman, M.S. (1990) Effects of soil on the dermal bioavailability of *m*-xylene in male rats. Environ. Res. 51:182-193.

Solomon, A.; Lowe, N.J. (1979) Percutaneous absorption in experimental dermal disease. Br. J. Dermatol. 100:717-722.

Southwell, D.; Barry, B.; Woodford, R. (1984) Variations in permeability of human skin within and between specimens. Int. J. Pharmaceut. 18:299-309.

Storm, J.E.; Collier, S.W.; Stewart, R.F.; Bronaugh, R.L. (1990) Metabolism of xenobiotics during percutaneous penetration: role of absorption rate and cutaneous enzyme activity. Fundam. Appl. Toxicol. 15:132-141.

Stoughton, R.B. (1975) Animal models for in vivo percutaneous absorption. In: Maibach, H.I., ed. Animal models in dermatology. Edinburgh: Churchill Livingstone; pp. 121-132.

Stoughton, R.B., Clendenning, W.E.; Lruse, D. (1960) Percutaneous absorption of nicotinic acid and derivatives. J. Invest. Dermatol. 35:337.

Surber C.; Wilheim, K.P.; Hori, M.; Maibach, H.I.; Guy, R.H. (1990a) Optimization of topical therapy: partitioning of drugs into stratum corneum. Pharm. Res. 7(12):1320-1324.

Surber, C.; Wilhelm, K.P.; Maibach, H.I.; Hall, L.L.; Guy, R. H. (1990b) Partitioning of chemicals into human stratum corneum: implications for risk assessment following dermal exposure. Fundam. Appl. Toxicol. 15:99-107.

Tarshis, B. (1981) The "Average American" Book. New York, New American Library; pp. 191.

Tauber, U.; Rost, K.L. (1987) Esterase activity of the skin including species variations. In: Shroot, B.; Schaefer, H., eds. Pharmacology and the skin, Vol.1, Skin pharmacokinetics. Basel, Switzerland: Karger, P.; pp. 170-183.

Taylor, E.A. (1961) Oral absorption: a method for determining the affinity of skin to absorbed oil from aqueous dispersion. J. Invest. Dermatol. 87:69-72.

Thibodeaux, L.J. (1979) Chemodynamics. New York, NY: John Wiley and Sons, Inc.

Thohan, S.; Barr, J.; Sipes, I.G. (1989) Metabolism of 7-ethoxycoumarin (7-EC) by adult F-344 rat skin. Toxicology 9:240.

Tojo, K.; Lee, A.C. (1989) A method for predicting steady state rate of skin penetration in vivo. J. Invest. Dermatol. 92:105-108.

Tregear, R.T. (1966) Physical functions of skin. New York, NY: Academic Press; pp. 1-52.

Treherne, J.E. (1956) The permeability of skin to some nonelectrolytes. J. Physiol. 133:171-180.

Tsuruta, H. (1975a) Percutaneous absorption of organic solvents. I. Comparative study of the in vivo percutaneous absorption of chlorinated solvents in mice. Ind. Health 13:227-236.

Tsuruta, H. (1975b) Percutaneous absorption of trichloroethylene in mice. Ind. Health 16:145-148.

Tsuruta, H. (1977) Percutaneous absorption of organic solvents. II. A method for measuring the penetration rate of chlorinated solvents through excised rat skin. Ind. Health 15:131-139.

Tsuruta, H. (1982) Percutaneous absorption of organic solvents. III. On the penetration rates of hydrophobic solvents through the excised rat skin. Ind. Health 20:335-345.

Tsuruta, H. (1986) Percutaneous absorption of chemical substances and toxicity--especially about organic solvents. Eisei Kagaku 32:229-241.

Tsuruta, H. (1989) Skin absorption of organic solvent vapors in nude mice in vivo. Ind. Health, 27:37-47.

Valia, K.; Chien, Y. (1984a) Long-term skin permeation kinetics of Estradiol. I. Drug Develop. Ind. Pharm. 10:951-981.

Valia, K.; Chien, Y. (1984b) Long-term skin permeation kinetics of Estradiol II. Drug Develop. Ind. Pharm. 10:991-1015.

Wadden, P.A.; Scheff, P.A. (1983) Indoor air pollution: characterization, prediction, and control. New York, NY: John Wiley and Sons.

Wahlberg, J.E. (1965a) Some attempts to influence the percutaneous absorption rate of sodium (^{22}Na) and mercuric (^{203}Hg) chlorides in the guinea pig. Acta Derm. Venereol. 45:335-343.

Wahlberg, J.E. (1965b) Percutaneous absorption of sodium chromate (^{51}Cr) cobaltous (^{58} Co), and mercuric (^{203}Hg) chlorides through excised human and guinea pig skin. Acta. Derm. Venereol. 45:415-256.

Wahlberg, J.E. (1968) Percutaneous absorption from chromium (^{51}Cr) solutions of different pH, 1.4-12.8. Dermatologica. 137:17-25.

Wahlberg, J.E. (1970) Skin clearance of iontophoretically administered chromium (^{51}Cr) and Sodium (^{22}Na) ions in the guinea pig. Acta Derm. Venereol. 50:225-262.

Wahlberg, J.E. (1971) Vehicle role of petrolatum. Absorption studies with metallic test compounds in guinea pigs. Acta Derm. Venereol. 51:129-134.

Wahlberg, J.E.; Skog, E. (1962) Percutaneous absorption of mercuric chloride in guinea pigs. Acta Derm. Venereol. 42:418-425.

Wahlberg, J.E.; Skog, E. (1963) The percutaneous absorption of sodium chromate (51Cr) in the guinea pig. Acta Derm. Venereol. 43:102-108.

Wahlberg, J.E.; Skog, E. (1965) Percutaneous absorption of trivalent and hexavalent chromium. Arch. Derm. 92:315-318.

Walker, M.; Dugard P.H.; Scott, R.C. (1983) In vitro percutaneous absorption studies: a comparison of human and laboratory species. Hum. Toxicol. 2:561.

Wester, R.C.; Maibach, H.I. (1976) Relationship of topical dose and percutaneous absorption in rhesus monkey and man. J. Invest. Dermatol. 67:518-520.

Wester, R.C.; Maibach, H.I. (1983) Cutaneous pharmacokinetics: 10 steps to percutaneous adsorption. Drug Metab. Rev. 14(2):169-205.

Wester, R.C.; Maibach, H.I. (1986) Dermatopharmacokinetics: a dead membrane or a complex multifunctional viable process. Prog. Drug Metab. 9:95-109.

Wester, R.C.; Maibach, H.I. (1989a) Skin contamination and absorption of chemicals from drinking water while bathing or swimming. In: Bronaugh R.L.; Maibach, H.I., eds. Percutaneous absorption: mechanisms, methodology, drug delivery. 2nd ed. New York, NY: Marcel Dekker; pp. 191-196.

Wester, R.C.; Maibach, H.I. (1989b) Human skin binding and absorption of contaminants from ground and surface water during swimming and bathing. J. Am. Coll. Toxicol. 8(5):853-859.

Wester, R.C.; Bucks, A.W.; Maibach, H.I.; Anderson, J. (1983) Polychlorinated biphenyls (PCBs): dermal absorption, systemic elimination and dermal wash efficiency. J. Toxicol. Environ. Health 12:511-519.

Wester, R.C.; Maibach, H.I.; Surinchak, J.; Bucks, D.A.W. (1985) Predictability of in vitro diffusion systems. Effect of skin types and ages on percutaneous absorption of triclocarban. In: Bronaugh R.L.; Maibach, H.I., eds. Percutaneous absorption. New York, NY. Marcel Dekker; pp. 223-226.

Wester, R.C.; Mobayen, M.; Maibach, H.I. (1987) In vivo and in vitro absorption and binding to powdered stratum corneum as methods to evaluate skin absorption of environmental chemical contaminants from ground and surface water. J. Toxicol. Environ. Health 21:367-374.

Wester, R.C.; Maibach, H.I.; Bucks, D.A.W.; Sedik, L.; Melendres, J.; Liao, C.; DiZio, S. (1990a) Percutaneous absorption of [^{14}C]DDT and [^{14}C]Benzo[a]pyrene from soil. Fund. App. Toxicol. 15:510-516.

Wester, R.C.; Maibach, H.I.; Bucks, D.A.W.; McMaster, J.; Mobayen, M. (1990b) Percutaneous absorption and skin decontamination of PCBs: in vitro studies with human skin and in vivo studies in the rhesus monkey. J. Toxicol. Environ. Health 31:235-246.

Wester, R.C.; Maibach, H.I.; Sedik, L.; Melendres, J.; DiZio, S.; Jamall, I.; Wade, M. (1991) In vitro percutaneous absorption of cadmium from water and soil. Toxicol. 11:289. Abstracts of the 30th Annual Meeting.

Wieczorek, H. (1985) Evaluation of low exposure to styrene. II. Dermal absorption of styrene vapors in humans under experimental conditions. Int. Arch. Occup. Environ. Health 57:71-75.

Yang, J.J.; Roy, T.A.; Mackerer, C.R. (1986a) Percutaneous absorption of benzo[a]pyrene in the rat: comparison of in vivo and in vitro results. Toxicol. Ind. Health 2(4):409-415.

Yang, J.J.; Roy, T.A.; Mackerer, C.R. (1986b) Percutaneous absorption of anthracene in the rat: comparison of in vivo and in vitro results. Toxicol. Ind. Health 2(1):79-84.

Yang, J.J.; Roy, T.A.; Krueger, A.J.; Neil, W.; Mackerer, C.R. (1989) In vitro and in vivo percutaneous absorption of benzo[a]pyrene from petroleum crude-fortified soil in the rat. Bull. Environ. Contam. Toxicol. 43:207-214.

Yano, T.; Nakagawa, A.; Tsuji, M.; Noda, K. (1986) Skin permeability of various non-steroidal anti-inflammatory drugs in man. Life Sci. 39:1043-1050.

Zatz, J.L. (1983) Fundamentals of transdermal controlled drug administration: physicochemical considerations. Drug. Dev. Ind. Pharmacy 9(4):561-577.

Zendzian, R.P. (1989) Skin penetration method suggested for Environmental Protection Agency requirements. J. Am. Coll. Toxicol. 8(5):829-835.

Zesch, A.; Nitzche, K.N.; Lange, M. (1982) Demonstration of percutaneous resorption of a lipophilic pesticide and its possible storage in the human body. Arch. Dermatol. Res. 273(1-2):43-49.

★U.S. GOVERNMENT PRINTING OFFICE: 1992-648-003/41805